The New England
Journal of Medicine

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Volume 240 FEBRUARY 10, 1949 Number 6

ELECTROSHOCK THERAPY IN DEPRESSIVE STATES*

Experience in a General Hospital

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SINCE its introduction by Cerletti and Bini[1] in 1938, electroshock therapy has become an accepted therapeutic procedure and has replaced metrazol as the most effective therapeutic convulsive agent. It has been found most useful in depressive states of a manic depressive nature, involutional depressions and involutional paranoid conditions and in depressions of later life and also as an adjunct in the treatment of psychoneuroses with depressive coloring. It has replaced insulin in the treatment of some early cases of schizophrenia, and has been used experimentally in a large variety of neuropsychiatric conditions including general paresis,[2] Parkinson's disease,[3] tics,[3] stammering,[4] drug addiction and alcoholism,[5] with indifferent results in many cases.

Electroshock treatment has been mostly limited to state psychiatric institutions and private psychiatric hospitals and occasionally ambulatory office treatment of well behaved, co-operative patients. The office treatment has been frowned upon,[6] however, in view of the inadequacy in most cases of office facilities for close supervision of patients during and after treatment and the danger of an unexpectedly fatal outcome or the development of severe complications. Such emergencies as respiratory embarrassment, acute disturbed postconvulsive states, fractures or dislocations may be difficult to manage in a physician's office. Authorities in general hospitals have also been reluctant to admit any patients even with mild psychiatric disorders for psychiatric treatment, although the same patients were frequently admitted for a surgical procedure or medical care without hesitation. The reason usually given was that adequate facilities were not available for proper care of such patients in the hospital, and also that the presence of these patients might become upsetting to others. Although it must be admitted that hospitalization of an agitated patient for prolonged psychiatric treatment in a general hospital in the present crowded condition of such hospitals might arouse justifiable criticism, the hospitalization of a patient for a course of electroshock therapy for a period of ten days or two weeks should not be considered any different from hospitalization for a surgical operation. The urgency is just as great in one case as in the other, and in the communities where no adequate private psychiatric facilities exist this is at times a godsend.

The Elliot Hospital in Manchester and the Concord Hospital have been accepting patients for electroshock therapy for several years, and so far the hospital authorities have had no reason to regret this decision. It was found that some patients in a mildly agitated and apprehensive state could be safely handled in a ward or in a private room till after the first or second electroshock treatment. Usually, the agitation subsides after a few treatments and the improvement that follows often makes close supervision unnecessary.

The advantage of treatment in a general hospital is that any additional studies such as electrocardiograms, x-ray studies and urine and blood examinations can be carried out whenever indicated, without the need of transferring the patients to a general from a psychiatric hospital for such studies as is occasionally the procedure. Also, services of consultants, including cardiologists, orthopedic surgeons and bronchoscopists, are readily available if the need should arise. The fact that the depressed patient can enter a general hospital for special treatment has acted as an emotional booster after recovery has taken place, in that it helped to remove the stigma of admission to a specialized "insane" hospital for treatment, and the emotional trauma that is occasionally associated with such an experience is thus obviated.

The psychiatrist benefits from the hospitalization in that any psychotherapy indicated can be carried out while the patient is in the hospital, and the hospital resident medical and nursing staffs

*Presented at the annual meeting of the New Hampshire Medical Society, New Castle, New Hampshire, June 2, 1948.
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can often be utilized for added indirect psychotherapy. From a teaching point of view, the medical residents can see these patients and follow up their progress and response to treatment. No special facilities are required except a room with a Gatch bed, electroshock apparatus and a nursing team. One nurse assistant experienced in electroshock therapy is sufficient, and usually other nurses can be recruited easily from the regular nursing staff.

The usual number of treatments given to patients that I have treated has been five to seven administered every other day. When electroshock therapy was first introduced it was deemed advisable to administer twelve to twenty treatments as a minimum to most patients in a depressive state. The greatest number of treatments is still being used by many psychiatrists, but I have found that if the patient is going to improve, the major gains generally become apparent after the fourth or fifth treatment and the gain after subsequent treatments is often only minor. I have found it safe to discharge hospitalized patients after such a brief course of treatment, if in the opinion of a responsible member of the family the patient has reached the prepsychotic level. However, in depressed patients with paranoid delusions of long standing a greater number of treatments may be required to prevent a relapse.

The average hospitalization time was about fourteen days for out-of-town patients. Local residents with a satisfactory home environment and an understanding and co-operative family have been treated on an ambulatory basis, the patients remaining in the hospital for several hours after the treatment was completed to assure complete recovery from its aftereffects before they were allowed to leave for home in the company of a member of their family. All hospitalized patients are seen within a week of discharge from the hospital and are followed up at regular intervals. The family is also advised to communicate with the physician immediately if any untoward change takes place in the patient's condition.

I have found electroshock therapy most useful in cases of involutional melancholia and depressive reactions, either manic depressive or reactive depressions. The recovery rate has been raised in these cases, and the duration of the illness reduced about 75 per cent. It is now possible in many cases to abort a depressive attack with five or six electroshock treatments in a period of two weeks instead of the average duration in the past of from six to eighteen months.

Patients with involutional melancholia, who were formerly treated for long periods with estrogens without striking results and who either recovered on their own after several years of illness or finally required hospitalization in a psychiatric hospital, now show an 85 per cent incidence of recovery following electroshock therapy. Relapses have been uncommon in the cases treated, and in the relapsed cases an unsatisfactory home environment, which often was beyond the psychiatrist's control, contributed to the relapse. Recurrence of depressive attacks in patients treated with shock therapy is not greater than in those who recovered under conservative therapy, and in some patients prone to recurrences this can be aborted by the administration of one or more treatments regularly at monthly or bimonthly intervals.

I have also found electroshock therapy of value in early cases of schizophrenia, in selected cases of anxiety and conversion hysteria, especially those with depressive features, and also in 2 cases of obsessive compulsive neurosis in which the patients failed to improve under conservative therapy; the procedure was used as a remedy of desperation in these cases. In another case the therapy was administered when the patient had failed to improve after prolonged hospitalization in a psychiatric hospital. The obsessive fear of handling knives and compulsion of having to cause harm to members of her family had resulted in the patient's separation from her younger children for several years. The intensity of the fears and compulsions became greatly reduced after five electroshock treatments. In the end she was able to discuss these fears in an impersonal manner, and although they did not entirely disappear she did not seem to be troubled by them to any extent and was able to resume full care of her children.

The oldest patient treated was seventy-two and the youngest twenty years old. Age is no contraindication to treatment, and many depressions of later life respond well to electroshock therapy. One patient had auricular fibrillation and also a right-sided hemiparesis. She was exhausting herself physically from her continuous agitation, impaired sleep and worry over real and imaginary transgressions in the past. The cardiac consultant believed that in view of her poor prognosis without treatment as far as her cardiac condition was concerned, the risk of electroshock treatment was worth taking. She tolerated the treatments well. At the end of a course of six treatments the agitation subsided, self-accusatory ideas disappeared, and she was able to resume her normal activities. Her heart function also improved with the removal of contributing psychogenic factors. The hemiplegia was not aggravated by the treatment, and a constant, severe pain in the paralyzed shoulder of which she complained before treatment also disappeared.

There have been no serious complications in any of the cases treated. It is a safe procedure when properly supervised and the mortality is no greater than that for a general anesthetic. In a survey of deaths from electroshock therapy in all American hospitals, Kolb and Vogel[7] found a mortality figure of 6 per 10,000 or about one tenth the death rate for patients treated with insulin shock. The mor-

tality is slightly higher, however, in curare-treated cases, and many psychiatrists limit the use of curare to patients with suspected brittle bones, pre-existent fractures or extreme muscularity. I have used it only when there was a potential danger of bone fractures or in very muscular patients.

Postconvulsive excited states can be avoided in most cases by intravenous injection of 0.3 to 0.5 gm. of sodium amytal about ten or fifteen minutes before treatment. This complication occurred in 2 male patients and was relieved by sodium amytal injections. I have been taking this precaution routinely in strong, muscular persons who showed any evidence of excitement after the first treatment to avoid injury to the patient during this confused state.

Memory impairment is also a frequent transitory complaint, and its severity parallels the number of treatments administered. It usually clears up in a period of several weeks, and impairment is greatest in fields of recall and concentration. Respiratory embarrassment is more common in the curare-treated cases, although I have observed none in the cases I have treated so far. The use of a respirator or artificial respiration generally restores breathing to normal.

No fractures occurred in any of the cases treated. Dislocation of the jaw occurred in the same patient on two occasions and was easily reduced before this patient regained consciousness.

Case Reports

Case 1. M. M., a 21-year-old woman, had felt depressed for about 3 months, lost interest in her friends, slept poorly and expressed death wishes. She planned to be married in a month, but failed to take any interest in the arrangements for her wedding. She also gave up her work at the onset of her illness. Before the present symptoms came on she had had a period of overactivity when she talked excessively, was flighty in her ideas, wanted to be on the go, had many plans, made some foolish purchases and spent her money lavishly.

During the psychiatric interview she was slow in her responses, was unable to elaborate on her symptoms and gave perfunctory answers. She complained of having lost her ambition and said she did not care whether her forthcoming marriage was to take place. She admitted feeling depressed and wishing she were dead. After the second electroshock treatment she talked more freely about herself, appeared more cheerful and showed interest in ward routine and in other patients. After the fifth treatment she developed a mild hypomanic state when she laughed out without evident cause, had a number of plans for her wedding and appeared exuberant and full of energy. This phase subsided in 2 days. She was discharged from the hospital 2 weeks after admission, appearing "like her usual self," according to her parents. She showed good judgment and insight during follow-up interviews, and was reported to be in good mental health a year after her discharge from the hospital.

The diagnosis was that of a manic depressive, depressive reaction, with good recovery following electroshock therapy.

Case 2. L. D., a 45-year-old woman with a diagnosis of involutional melancholia, had been depressed for about 1 year and had given up her job as a business executive 6 months earlier. She blamed this action on her inability to concentrate, fears of losing her mind and continuous preoccupation and guilt feeling over poor business investments (the last being untrue). She received estrogen injections for over 1 year without improvement. She recovered after five electroshock treatments, and was able to return to work 5 weeks after the treatments were begun. She was treated on an ambulatory basis. She had continued in good mental health for 1 year after the treatments had been completed.

Case 3. G. G., a 49-year-old woman, had been depressed, self-accusatory and apprehensive for 2 years. She became obsessed with many religious ideas, blamed herself for the neglect of her family and refused to allow her husband to go to work for fear of some harm befalling him when he was away from her. She had received estrogenic therapy, various sedatives, and iron and liver for her anemia, without improvement.

When she was admitted she was very apprehensive, and it was doubted whether she could be cared for in a general hospital. Much persuasion had to be used before the first treatment could be given. After this treatment she appeared more relaxed and co-operated well in the other five treatments. She made an excellent recovery after 2 weeks of hospitalization, and has been doing her housework, and her own shopping, which she did not do before admission for treatment. The self-accusatory ideas have disappeared, and she shows good insight. Her husband has also been able to return to his job. As she described it "she has not felt so well for years." She complained of some impairment of memory for several weeks after her return home, which was somewhat annoying at first, but later she found that by taking her time she had no difficulty whatsoever in recalling past events.

The diagnosis was that of involutional melancholia, with good recovery.

Case 4. J. N., a 57-year-old man, developed what he described as a nervous breakdown 2 years previously. He felt discouraged, worried about the loss of his job, failed to enjoy doing things that gave him much pleasure in the past and blamed himself for neglect of his family and his job. He was treated with testosterone, sedation and vitamins, but symptoms continued and he had to give up his job. He had had a "nervous breakdown" 14 years earlier, which lasted a number of months.

Electroshock therapy was recommended, but he believed that he could benefit more from a few months of rest on a farm. After he failed to improve under this regime, he was given four electroshock treatments, for which he was hospitalized for 2 weeks. He tolerated the treatments well except for a postconvulsive excited period, which lasted for about 10 minutes after the second treatment. He made an excellent recovery and returned to work 10 days after leaving the hospital and has been regularly employed since. The anhedonia and self-accusatory ideas have disappeared, and he enjoys all his former activities.

The diagnosis was that of recurrent depressive reaction with involutional features.

Discussion

It has been estimated that for a community with a population of about 100,000 an average of 12 psychiatric beds set apart in the general hospitals in that community would be a minimum requirement.[8] When one considers that only about 1 in 5 new patients admitted to a state hospital require care on a disturbed ward, and that early diagnosis and treatment frequently aid in aborting a psychotic attack or reduce its severity so that such a patient can be adequately cared for in a general hospital, it becomes obvious that the better the facilities in a general hospital for the care of such patients, the lighter the burden for the state hospital.

The advantages of general-hospital care are that the hospital stay is greatly reduced for the reason that patients are usually worked up faster and any treatment needed is immediately applied. There has been a tendency in state hospitals because of

shortage of staff physicians and for other reasons to postpone treatment in new admissions till a staff diagnosis is made, which often delays active treatment for some time. At comparatively little cost in even the smaller hospital several rooms can be easily remodeled to give adequate temporary care to any acute psychiatric emergency that might arise without disturbance to other patients. Acute confused and excited episodes are not too infrequent after surgical procedures, or deliveries, in cases of acute cardiac decompensation, anemias and other blood dyscrasias and in cases of cerebral metastatic neoplastic growths. If better facilities were available for the care of such patients in a general hospital, the need for transfer of patients with acute cardiac disorders some distance to a state hospital during a disturbed episode would be avoided. Not infrequently, such patients arrive at the hospital in a moribund condition and die shortly after arrival, much to the chagrin of the state-hospital staff. Attention has been called to this situation and also to the fact that a physician may become liable for malpractice for the unwarranted transfer of a patient to another hospital when the patient's condition is apt to suffer from such a change.[9] It has been planned, therefore, for at least four rooms to be set apart and equipped at the new unit of the Elliot Hospital for the care of any acute and subacute psychiatric problems that show promise of rapid improvement under proper care.

The mode of action of electroshock therapy is still unknown. Most likely it acts as a bloodless frontal lobotomy, reversible if a moderate number of treatments are given, and just as severe in its aftereffects after too many treatments. The effects are probably not limited to the cortex alone, but also involve the autonomic centers in the midbrain, the pituitary body and, indirectly, the gonadal system. The extinction of undesirable patterns of behavior in animal experients has been described by Masserman and Jacques[10] after electroshock therapy — at the cost, however, of impairment of some of the higher integrative functions. If the psychosis or neurosis is sufficiently disabling and has not responded to conservative therapy, electroshock treatment appears to be preferable to continuation in the previous state even at the risk of some memory impairment.

There is still considerable divergence of opinion about the value of electroshock therapy in the psychoneuroses. I have seen cases of anxiety neurosis definitely aggravated by electroshock therapy administered elsewhere; improvement was observed after the shock therapy had been discontinued and the patient had been reassured that no more shock treatments were forthcoming and helped toward a better social adjustment, with special attention to sleep and nutritional habits. My impression is that the high rate of improvement reported by some observers[11] with electroshock therapy in cases of psychoneurosis is due to the fact that many of these patients really belong in the cyclic group of disorders, with the symptoms of anxiety and somatic discomforts actually representing a manic depressive, depressive equivalent. Such patients can often deceive even the best trained observer, and the somatic symptoms may be so vividly described and acted out by the patient that the patient often parts with a different organ with each depression at the hands of some eager surgeon. Not infrequently, recovery follows each surgical procedure, as a result either of the effects of the anesthesia (or the emotional release associated with feelings of penance and sacrifice that accompany organ removal in some persons) or the patient's removal to the restful, friendly and solicitous hospital atmosphere from an uncongenial home environment; the recovery may be due to a combination of all factors. These cases are often diagnosed as psychoneurosis, and no doubt the patients benefit from electroshock therapy in that the attacks can be aborted, although the incidence of recurrence is not affected by the treatment. In my own experience electroshock therapy is indicated in about 5 to 10 per cent of cases of psychoneurosis and should then be used only after the patient has failed to improve under a combination of psychiatric treatment, attention to somatic needs, vitamin therapy and betterment of domestic and social adjustment.

Summary and Conclusions

Electroshock therapy is a valuable therapeutic agent in cases of involutional depressions, cyclic depressive states, reactive and late life depressions and early cases of schizophrenia. It effects recovery in about 85 per cent of patients with involutional depression and, when administered early, aborts or greatly shortens the duration of manic depressive, depressive attacks, thus aiding in reducing hospitalization time, shortening the duration of disability and preventing suicidal attempts.

It is of value in selected cases of psychoneurosis, and should be used only in resistant cases after other methods of treatment have failed to cause improvement.

The utilization of general-hospital facilities for intramural and ambulatory electroshock therapy has not only brought relief to patients who would otherwise have refused treatment because of their reluctance to enter a psychiatric hospital but also acted as a morale builder to these patients by removing the feeling of ostracism that occasionally is still associated with hospitalization in a psychiatric hospital.

It is recommended that even the smaller general hospitals have one or more rooms equipped for the treatment of acute mildly disturbed psychiatric problems offering a good prognosis and amenable to rapid treatment. Such facilities if more widely

used would eventually aid materially in relieving some of the load in overcrowded state and private psychiatric hospitals.

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PRESIDENTIAL ADDRESS*

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MANY of the senior group of this society have had the rare opportunity of observing the growth of the art and science of modern surgery from a scope that, judged by present standards, was extremely limited to its present almost unbelievable heights. This development has carried with it serious responsibilities to the surgical profession, and also grave problems in the training of prospective surgeons to cope with the highly diversified and technical procedures that it will be necessary for them to master if they are to take their place as specialists in surgery. There have also been problems of raising the standards of hospital care, expansion of laboratory facilities and refinements of record systems and the limitation of incompetent and unnecessary surgery.

Volumes have been written and published through the years by leaders in the surgical field dealing with these problems. The efforts of the American College of Surgeons and, later, of the American Board of Surgery have been of inestimable value in correcting many of the existing weak spots in the practice of surgery However, many phases of the situation have not been, and probably cannot be, reached by these bodies without a fuller program, and definitely more decisive action by organized groups of surgeons who are in a position to mold the conscience and ideals of surgeons in general in their sphere of influence — for example, the New England Surgical Society in New England.

One hesitates to speak on the training of surgeons before a group who have recently listened to the excellent papers by Lanman[1] and Harvey[2] on this subject. These men have admitted that the training of surgeons has become too great a load for the teaching hospitals and although many references have been made to the possibility of training surgeons in the smaller hospitals, no positive action has been taken to supplement these suggestions. After forty years of surgical practice in a smaller community, one develops some ideas on this subject, and I hope to present to you a plan, and I use this word guardedly, that may eventually bring the outlying medical communities into the orbit of teaching institutions.

Until recently, there have been two schools of surgical teaching in this country: the prolonged period of carefully supervised training in teaching hospitals and clinics, and the method of trial and error used by general practitioners to perfect themselves gradually in the art of surgery. It was standard practice some years ago for a physician to begin in general practice and work into surgery gradually, and, had it not been for this self-training, much of the necessary surgery in the smaller hospitals would have gone undone. Today, such a practitioner has to ask a fully qualified surgeon to assist him in operations on appendixes, hernias and gall bladders and up the scale until he has developed enough dexterity to operate fairly safely. And all the while that the senior surgeon is keeping him out of trouble and guiding him through the maze of surgical technic and postoperative care, the novitiate collects the fee and poses as the surgeon. Today, such a practice is unnecessary, and all too often exploits the surgeon who is asked to assist. The American Board of Surgery and American College of Surgeons have done much to discourage this practice by listing minimal requirements of training before a physician is admitted to the surgical staff of a hospital. But the practice will not disappear until every recognized hospital adheres rigorously to these requirements.

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

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When more and more hospitals close their doors to the surgeon of subminimal requirements, it means that the smaller hospitals are no longer instrumental in training surgeons as they have been in the past, and a correspondingly heavy load is being thrown on the large training centers. Some plan whereby the smaller medical communities can be enlisted again in the training of surgeons who measure up to the high standards that are demanded must now be evolved.

Before any plan is outlined, it must be known what sort of surgeons are to be developed. The surgeon who has completed his residency, qualified for his board examinations and then settled in a large metropolitan area will restrict his surgical practice from the outset to some special field. If he ventures to a community with a small hospital, he will naturally seek to limit himself to surgery, but he cannot be so restricted as his city brethren. He will mainly be a consultant, for patients will not normally turn to him at once, but will be referred by the general practitioners, who see the bulk of patients when they are first taken sick.

The smaller communities cannot support specialists in every field — gynecology, urology, orthopedics, abdominal surgery and so forth, nor can a surgeon expect to keep very busy if his training has been limited to abdominal surgery. From the standpoint of the general practitioner, a surgical consultant must be able to deal with a wide variety of cases if he is to be of any great value to the medical community.

This imposes on the plan of training for the general surgeon a specific obligation, which is not fully recognized, if one is to judge by present trends. More and more, cases are segregated into special services. The young surgeon in his hospital training develops into what might well be called a glorified belly artist. He can remove an appendix or gall bladder and resect a stomach or rectum, but, all too often, the female pelvic organs, the prostate gland and the broken bone are terra incognita. Only if the young surgeon is willing to spend extra years in the larger hospitals can he develop a competence in general surgical work, which the small community needs and the general practitioner demands from the consultant in surgery.

Surgical leaders would do well to insist on rotation through special services by all the young surgeons. This does not mean rotation in menial tasks — a *leitmotif* of intravenous therapy, blood counts and postoperative care — but training that develops both manual dexterity and operating poise in all the common surgical conditions. Under such a system, it would be impossible to produce a situation such as recently came to my attention: a young surgeon had qualified for the American Board of Surgery and yet had no formal training in gynecologic surgery, which comprises 30 to 60 per cent of the practice for the general surgeon in the smaller community.

What I am saying has been expressed repeatedly by leaders in the specialties such as gynecology, obstetrics, orthopedics and urology. These men openly admit that the best practitioners of their particular arts have first of all a broad training in general surgery, so that, whether a man intends to go out to a smaller hospital or remain in the larger centers, his *basic* training should be essentially the same.

The smaller medical community has often glaring deficiencies in surgical service that could well be corrected by incoming surgeons of the younger generation. Perhaps an outside consultant is called in for thoracic cases or difficult fractures or plastic surgery. If the most recent addition to the surgical department can fill any existing gap in surgical talent, his path will be so much easier, and his acceptance by the staff less restrained.

This imposes on the surgeon who contemplates a move to the smaller hospitals the duty of acquainting himself intimately with the medical talents in the community where he plans to practice. Such knowledge will stimulate him to develop special ability in some limited field in addition to his broader training.

Is it possible to fit the smaller hospital into such a program of training? One must not be too impressed by size, for the "sticks" does not so much describe a geographic location as it does a state of mind. It is well to remember that patients in the mountains of New Hampshire and in the fishing villages of Maine have exactly the same diseases as those in Providence or Hartford. Wherever a surgeon takes a careful history, does a thorough examination and makes the necessary x-ray and laboratory studies for an intelligent working diagnosis, sound medicine is practiced, and there the student of surgery can learn and be trained.

A far more delicate subject is the level at which the smaller hospital shall assist in training surgeons. A plan that seems favored by some authors on this subject is to have surgeons train as interns for two or three years in the large center and then finish their apprenticeship in the smaller hospital.

The last part of a surgical training, or the resident stage, is by far the most important. It is the great climax for which all the previous years are but a preparation. The self-confidence, poise and judgment that are essential in the private practice of surgery are developed in this final phase. Smaller hospitals, with their more limited facilities, cannot complete the surgical training nearly as well as the large institutions at the last stage. If they are to be enlisted in the training program, it should be at the level of interns and assistant residents. Any plan that seeks to send men into practice before their training is fairly complete — that is, before their residency has been served — should be discouraged.

Surgery everywhere is a highly competitive field. One reason for this is that surgical fees are propor-

tionately much higher than those in other medical fields. Few of the thousands of doctors in this country who are engaged in private practice can afford to disregard the economic component of their profession. As a corollary, there is competition on two levels in surgery — the professional and the economic. Those who have enjoyed the superior training under men with working ideals usually place the professional consideration of competence first, and these high standards pertain particularly in academic circles. Above all, there is need for a program for training surgeons who can compete with the skills taught them by emphasis on good deeds, and who can succeed so well that they can prosper economically without stooping to unethical practices. All too often the greatest stumbling block in the path of a competent young surgeon who wishes to practice according to the highest ethics is an unscrupulous older colleague who attempts to shut him out.

Such a person may be a good surgeon with a jealous disposition, but usually he is one who uses the knife consistently as a diagnostic instrument of first recourse, and deliberately blames every poor result on the patient's disease. He is willing to continue his indiscriminate surgery even though he clearly realizes his own surgical imperfections.

When such a person (or a group of such men) gains control in a medical community, the place is not favorable to the healthy development of a younger surgeon who may have an excellent training. He is restricted at the outset; every poor result is magnified, and all too often, he is driven in despair to adopt exactly the same methods as his older colleagues.

Let the leaders in the medical centers sound out their young graduates who have settled in the smaller communities, and I am certain that they will find this to be about the greatest obstacle to good surgery that the young surgeon faces.

Some solution to this problem is necessary if openings for the younger generation of surgeons are to be developed, and if the smaller hospitals are to be enlisted in the training program. Here is a problem for the trustees of the hospital. The terrible frustration of talent and training that obtains in many smaller hospitals will not be remedied unless the tactics of the vested interests are curbed by the hospital trustees.

One can expostulate on what should be and on the changes to be made, but no plan that involves the small hospitals will ever succeed without a full and active support from the trustees. Theirs is the power to set standards that will attract the best talent of the community; conversely, if they allow anyone and everyone to do surgery, they will discourage the most competent.

The hospital trustees are selected in various ways, but, by and large, they are local citizens with a record of good business ability. These men are often fully occupied with their business duties, and the hospital is a charity service that they assume as an obligation to the community. If the bills are paid and the hospital is quiet and clean, they believe that they have discharged their duties, and that the medical profession should be grateful for a place to work. To formulate some policy regarding professional practices in the hospital, they are heavily dependent on the director, who may be a physician, a layman with business training or a nurse who has climbed up from one administrative position to another until she has arrived at that of superintendent. Unless the director or some of the trustees make a special effort to enlighten themselves on such matters as surgical standards and the development of the best practices in the hospital, the staff finds itself floundering in *status quo*.

Hospital trustees need help in the form of sound and impartial advice if they are to keep their hospital apace of new standards in surgery, and if they dare not seek it locally, they should find it elsewhere in some competent consultant.

All the things that I have said are by way of formulating a plan for the training of surgeons in smaller hospitals. This purpose will be served best by an integrated plan that utilizes the smaller hospital as part of a training system. Smaller hospitals with such essential facilities as adequate x-ray equipment, a roentgenologist, laboratory facilities and a pathologist should affiliate with larger teaching hospitals. The staff of the parent hospital could serve as consultants to the smaller institutions, and also function as chiefs of service. Clinics and conferences in the teaching hospitals could be open to the staffs of the affiliated groups. By enlisting the support of the trustees for this plan, the smaller hospitals could develop such standards of personnel and practice that they could be trusted to help train interns or assistant residents in rotation from the teaching hospitals. In this way, the new generation would learn much about surgical practice in smaller communities and also find openings for themselves. The trustees might well ask the director of the central hospital to serve on a retainer-fee basis as consultant in local problems that seem difficult of solution.

In his presidential address last year, Dr. Lanman[1] hesitated to suggest the formation of another committee. I do not hesitate, but boldly submit that this society choose some members to make a careful study and formulate concrete proposals that can be adopted as a general program to support. The time has come to implement words about training surgeons in smaller hospitals with a realistic and workable plan.

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SALT-LOSING NEPHRITIS SIMULATING ADRENOCORTICAL INSUFFICIENCY*

Report of a Case

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THORN, Koepf and Clinton,[1] in 1944, reported 2 cases of renal failure simulating adrenocortical insufficiency. They called this syndrome "salt-losing nephritis." Symptoms such as asthenia, weight loss, nausea, vomiting and hypotension were observed and attributed to an excessive loss of sodium and chloride in the urine. Such salt loss was not due to a deficiency of adrenocortical hormones but to disease of the renal tubule, the end-organ on which such hormones act in controlling the reabsorption of sodium and chloride from the glomerular filtrate. The symptoms due to the salt loss were relieved by the administration of sodium, chloride and bicarbonate. The kidneys in these cases were demonstrated to be incapable of normal responses to desoxycorticosterone acetate (DOCA), to pituitrin or to the parathyroid hormone.

The case presented below is another example of salt-losing nephritis simulating Addison's disease. The presence of tanning of the skin, asthenia, weight loss, nausea, vomiting and hypotension, and the absence of cardiac enlargement, eye-ground changes or abnormal urinary constituents led at first to the diagnosis of Addison's disease. This was practically impossible to disprove before death. The presence of severe renal tubular insufficiency, however, with an inability to reabsorb salt in response to DOCA was readily demonstrated.

CASE REPORT

E. T., a 53-year-old married shoe salesman, first entered the hospital on March 11, 1947, complaining of weakness, weight loss and frequent vomiting following meals. He gave a history of mild diurnal frequency (five or six times) and nocturia (four or five times) for several years.

Seven years before admission he had entered another hospital for treatment of a bleeding duodenal ulcer. After this he had been essentially well for about 1 year. He then started experiencing epigastric pain between meals, relieved by food or alkali. Four years before admission he again entered the same hospital, complaining of gastrointestinal bleeding. At that time the blood nonprotein nitrogen was 319 mg. per 100 cc., and the urine contained albumin and white and red cells. After 1 month the nonprotein nitrogen had fallen to 92 mg. per 100 cc., and he was discharged.

One year before admission he again entered that hospital complaining of epigastric distress. The nonprotein nitrogen was 125 mg. per 100 cc., the urine showed a + test for albumin, and the sediment contained a few white cells. Five days later the urine was reported as completely normal. One month later the nonprotein nitrogen was 60 mg. per 100 cc., and he was discharged.

Physical examination revealed a thin, pale and weak man. The body weight was 128 pounds. The eye grounds appeared normal. The chest was clear. The heart was not enlarged on physical or x-ray examination. There was some tenderness deep in the epigastrium. The skin appeared diffusely tanned. There was no pigmentation of the mucous membranes.

The blood pressure was 120/70, and the pulse 96.

Examination of the blood disclosed a red-cell count of 2,800,000, with a hemoglobin of 8.7 gm. (photoelectric-cell technic), and a white-cell count of 10,000, with 59 per cent neutrophils. The blood Kahn reaction was negative. The nonprotein nitrogen was 159 mg., the creatinine 6.0 mg., the total protein 7.4 gm., and the blood chloride (as sodium chloride) 430 mg. per 100 cc.

A gastrointestinal series showed an irregular duodenal cap and moderate pyloric obstruction to the passage of barium. Intravenous pyelograms disclosed no visible excretion of the diodrast. An intravenous phenolsulfonephthalein excretion test revealed a total of 10 per cent excretion of the dye in 2 hours. A urine concentration test demonstrated a maximum specific gravity of 1.010. Fifteen routine morning urine specimens showed specific gravities ranging from 1.003 to 1.012. In one specimen the sediment contained rare red cells, and in several it contained from 1 to 8 white cells per centrifuged high-power field. At *no time was albumin or casts observed.*

After admission the patient showed no signs of gastrointestinal bleeding. He was placed on hourly administration of milk and cream and antacids. Vomiting, however, became severe, and constant suction was begun through a Levine tube introduced into the stomach. Large quantities of dextrose and saline solutions, 1500 cc. of plasma and 500 cc. of whole blood were administered intravenously during the first 2 hospital weeks. The suction was discontinued at the end of 5 days, and vomiting did not immediately recur. About 2 weeks after admission the blood pressure was 130/72, and the nonprotein nitrogen had fallen to 60 mg. and the blood creatinine to 3.2 mg. per 100 cc. The white-cell count was 5800, and the hemoglobin 8.7 gm. The patient remained relatively asymptomatic and gained about 10 pounds of weight during the ensuing month. During this time he began taking about 15 gm. of sodium bicarbonate daily for relief of mild epigastric distress.

Two months after admission he experienced more severe epigastric pain and repeated vomiting. He became extremely weak, the pulse became rapid, and the blood pressure fell to 80/60. He lost 12 pounds of weight in 1 week. The nonprotein nitrogen rose to 100 mg., and the creatinine to 7.5 mg. per 100 cc. The blood chloride (as sodium chloride) was 429 mg. per 100 cc. At this time the patient was seen by several medical consultants. The presence of diffuse tanning of the skin, nausea and vomiting, elevation of nonprotein nitrogen and creatinine, marked asthenia and weight loss led to a diagnosis of Addison's disease in crisis. The absence of known hypertension and of albumin and formed elements in the urine, the normal heart size and the normal eye grounds were all taken as indications that the patient did not have a significant degree of nephritis. Part 1 of the water diuresis test of Robinson, Power and Kepler[2] was performed and interpreted as being consistent with the diagnosis of Addison's disease. The night urinary volume was 1715 cc., and the maximum hourly urine specimen after the ingestion of water was 200 cc.

In view of the diagnosis of Addison's disease the patient was given 36 gm. of sodium chloride and 30 cc. of adrenocortical extract intravenously on May 21 and 22, and was started on desoxycorticosterone acetate in oil (DOCA) intramuscularly, 10 mg. a day. He continued to receive 15 gm. of sodium bicarbonate by mouth daily. The immediate response was dramatic (Fig. 1), the blood pressure rose in 3 days to 110/68, and the patient experienced marked subjective improvement. This was interpreted as added evidence for the presence of Addison's disease. Despite the continuation of 10 mg. of DOCA daily, however, as well as the 15 gm. of sodium bicarbonate, the symptoms of asthenia, nausea and vomiting returned. Over the course of 10 days

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the blood pressure again fell to 80/50. He was again treated with 20 cc. of adrenocortical extract and 18 gm. of sodium chloride given intravenously. He was also placed on 5 gm. of sodium chloride in enteric-coated capsules daily in addition to the dietary salt and 15 gm. of sodium bicarbonate orally. On this regime there was again a definite subjective improvement, and the blood pressure and body weight showed a more gradual but definite rise (Fig. 1).

At this point it was suspected that the patient had a salt-losing nephritis as described by Thorn, Koepf and Clinton.[1] Accordingly, on June 17, DOCA was discontinued. The patient continued to show a steady rise in blood pressure, body weight and feeling of well-being on sodium chloride and sodium bicarbonate given orally alone.

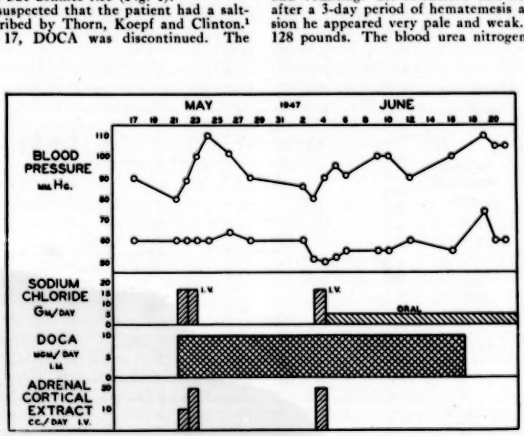

FIGURE 1. *Ineffectiveness of Desoxycorticosterone Acetate in Oil (DOCA), 10 mg. Intramuscularly Daily, in Maintaining the Blood Pressure of a Patient with Salt-Losing Nephritis.*

Since a patient with adrenal insufficiency alone might show similar improvement on this therapy an attempt was made to determine whether the kidney itself was unable to respond to the administration of DOCA. Urinary and blood chloride determinations, blood pressure and body weight were followed before, during and after the administration of a large daily dose (20 mg.) of DOCA for 7 days. The diet was kept constant during this period, and the patient continued to take 5 gm. of sodium chloride and 15 gm. of sodium bicarbonate orally. The results obtained are shown diagrammatically in Fig. 2. It appears that gains in body weight and blood pressure during this observation period, including the time before and after DOCA was administered, were quite steady and not greatly influenced by the administration of the drug. There was only a slight decrease in the concentration of urinary chloride from 650 to 600 mg. per 100 cc. (as sodium chloride) during the administration of DOCA, and the blood chloride level was not greatly altered.

A pituitrin concentration test, consisting of 10 units of pituitrin given subcutaneously, was performed, and the urine collected at one and two hours. The specific gravities of the specimens were 1.009 and 1.008 respectively. An intravenous glucose tolerance test was also performed, 0.5 gm. of glucose per kilogram of body weight being given intravenously over a 30-minute period. Blood glucose levels were as follows: fasting control 111 mg., 1 hour 167 mg., 2 hours 114 mg., 3 hours 87 mg., and 4 hours 83 mg. per 100 cc.

The patient continued to feel well on 5 gm. of salt and 15 gm. of sodium bicarbonate by mouth daily. The blood urea nitrogen was relatively stable at between 35 and 45 mg. per 100 cc. The carbon dioxide combining power ranged between 55 and 65 vol. per cent. The weight reached 127 pounds. He was discharged on August 23, with advice to continue taking the same amounts of salt and bicarbonate, to watch for the formation of edema, and to follow an intermediate ulcer diet. The diagnoses on discharge were salt-losing nephritis and duodenal ulcer, chronic, with partial obstruction.

He adjusted himself well at home on this regime but did not return to work. He followed the directions until about 4 months after discharge, when he again experienced epigastric pain and vomiting. He re-entered this hospital on December 9, after a 3-day period of hematemesis and melena. On admission he appeared very pale and weak. The body weight was 128 pounds. The blood urea nitrogen was only 37 mg., the creatinine 2.7 mg., and the blood chloride (as sodium chloride) 483 mg. per 100 cc. The urinary specific gravity was 1.007, and no formed elements or albumin was present. Repeated blood transfusions were given, but signs of slow bleeding continued. On December 26 a subtotal gastrectomy was performed as an emergency procedure. After operation the patient developed clinical and roentgenologic signs of pulmonary edema. The blood nonprotein nitrogen was 150 mg. per 100 cc., and the red-cell count 4,200,000. Despite oxygen, morphine, digitoxin and penicillin the signs of pulmonary congestion increased, and early on the morning of December 28, he had a single clonic convulsion and died.

At autopsy* there was a fresh midline upper abdominal scar. The skin was a diffuse light brown.

The pleural cavities contained about 550 cc. of pink fluid. The peritoneal cavity contained 100 cc. of red fluid. There was a recent gastric resection, and gastrojejunostomy. These anastomoses were firm and healing in good position. The duodenal stump was closed and covered with omentum.

The right lung weighed 1100 and the left 850 gm. They were firm and boggy in consistence. On section there was a tremendous amount of foamy pink fluid from all lobes and in the major bronchi.

The heart weighed 380 gm. There was dilatation of the right ventricle, and the coronary arteries were extensively calcified. There was moderate narrowing, but no occlusion of the vessels.

There were two ulcers in the duodenal stump. The remainder of the intestinal tract was normal except for large amounts of black fecal matter.

The liver weighed 2050 and the spleen 300 gm. Both showed chronic passive congestion.

The pancreas weighed 100 gm., the head was firm, and the body and tail were normal in color and consistence.

*Performed by Dr. Russell H. Pope.

The adrenal glands were greatly increased in size. The left weighed 21 gm. The right was torn during removal and could not be weighed but appeared similar in size to the left. The cortex was normal in color and about twice the normal width.

The kidneys were small, weighing 70 gm. each. The capsules stripped with difficulty. The surface was finely granular. The organs cut with increased resistance to the knife. The cortex was reduced in width, being about 3 mm. thick. The boundaries between cortex and medulla were indistinct. The pyramids were small but not flattened. The pelvic mucosa appreciable intimal disease. There were numerous cystic spaces surrounded by a heavy layer of pink-staining acellular material containing a blue-staining substance resembling calcium. These were located for the most part in the connective-tissue septums.

The kidneys, on multiple sections, demonstrated remarkably few functioning glomeruli. Nearly all were represented by hyaline balls, some of which showed blue-staining calcific precipitates. Occasional glomeruli appeared to be functioning, but even these revealed separation of the tufts, adhesions and marked thickening of Bowman's capsule. A

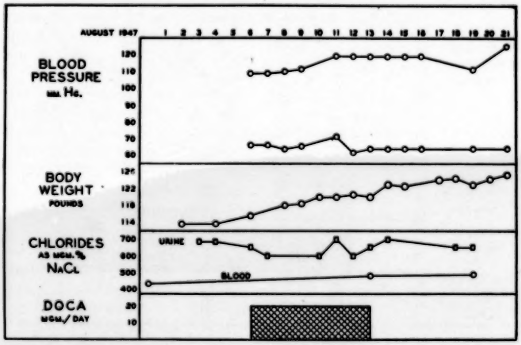

FIGURE 2. *Ineffectiveness of Desoxycorticosterone Acetate in Oil (DOCA), 20 mg. Intramuscularly Daily, in Significantly Altering the Blood Pressure, Body Weight and Urinary Excretion of Chloride in a Patient with Salt-Losing Nephritis.*

was smooth and white except for a few small petechial hemorrhages. The ureters, bladder and prostate appeared normal.

The thyroid and parathyroid glands, brain and spinal cord were not examined.

Microscopical examination of the lungs showed moderate dilatation of the alveoli. The alveolar septums were thickened in many areas, with definitely increased connective tissue. The ends of the septums were clubbed and contained round, dark-blue granules surrounded by dark-blue rings suggestive of calcium. Streaks of granular, dark-blue material were seen along some of the septums. Near the hilar region these granules were quite numerous and in places had been shed into the alveolar spaces. In these areas the alveolar walls appeared quite stiff and thickened, and calcific rings were apparent in the septums, sometimes surrounding an entire alveolus. Some of the smaller vessels showed extensive calcific deposits in the media. A rare foreign-body giant cell was seen surrounding the calcific granules. Many of the alveoli were filled with protein precipitates and comprised many large macrophages containing dark pigment. The vessels of the lung were greatly dilated.

The heart revealed definite hypertrophy of the muscle fibers; the interstitial spaces appeared swollen and vacuolated. The smaller arteries demonstrated slight calcific changes in the media. There were early calcific deposits at the base of the aortic valve. The coronary arteries showed only slight fibrous thickening of the intima without cholesterol deposits. The media just below the internal elastic membrane was completely replaced in a ring-like manner by heavy deposits of calcium, which were strictly limited to the media. This calcification extended from the ostia into the smallest arterioles.

The liver and spleen disclosed chronic passive congestion.

The larger vessels running through the parenchyma of the pancreas showed marked medial calcification without few disclosed partial hyalinization. The renal parenchyma was greatly altered by an increase in connective tissue and areas of round cells. Many of the tubules were atrophied, and the epithelial cells were small, clumped together and surrounded by a remarkably thickened basement membrane. In a few places this membrane took a dark-blue stain suggesting calcium. The calcification of the basement membrane was quite striking and was seen on all the sections. There were extensive calcium deposits of another type in every field. These consisted of a great number of dark-staining granules clumped together to form irregular masses. The pyramids were extensively calcified in this manner, and some of the hypertrophied tubules were filled with these calcific balls but for the most part they seemed to be in the interstitial spaces. The larger arteries showed a severe degree of medial calcification. The veins were distended. The entire parenchyma was much reduced in width. The pelvic and ureteral epithelium was normal.

The adrenal glands demonstrated a diffuse increase in the cortical area and several small hyperplastic nodules or adenomas. The cortex appeared twice as thick as normal. The medullary cells were normal except for moderate autolysis.

Sections of bone taken from the sternum revealed no noticeable changes in the bony trabeculae or marrow.

DISCUSSION

The post-mortem studies corroborated the diagnoses of chronic duodenal ulcer and renal disease without Addison's disease. The most interesting findings were the extensive deposits of calcium in the lungs, kidneys and pancreas and in

the media of the arteries, including the coronary arteries. The medial calcification could not be considered ordinary arteriosclerosis because of the definite lack of intimal changes in the larger arteries. It seemed to be a special form of calcification resembling Mönckeberg's sclerosis or senile arteriosclerosis. It has been described as due to calcinosis from various causes. The calcification in this case was not extensive enough to be considered calcinosis but falls into the group of cases with "metastatic calcification."[3] Most of these patients were emaciated with severe disease of the bones, but the patient in the case reported above had no bone disease. Similar lesions can be produced in animals with excessive doses of vitamin D, chronic alkalosis and hypochloremia.[4] The calcification of the tubular basement membrane in this case suggested a specific disease of the tubules in view of the presence of salt-losing nephritis. The extensive deposits of calcium in other tissues pointed to a more general metabolic dyscrasia. The cause of this was open to speculation. This dyscrasia may have been associated with the large amount of alkali consumed by the patient over a long period. The interstitial calcification of the kidneys is a common finding in chronic renal disease and undoubtedly resulted, at least in part, from local increased alkalinity of the renal tissues.

The cause of death was probably pulmonary edema and cardiac edema and dilatation due to an overloaded circulation following multiple transfusions for the shock of operation and the prolonged gastrointestinal hemorrhage.

This case bore a striking resemblance in many respects to the 2 reported by Thorn, Koepf and Clinton.[1] Only once during the last two periods of hospitalization did the patient show abnormal formed elements in the urine, and examination never disclosed albuminuria. Formed elements were notably absent in the urine in both the cases reported by Thorn, Koepf and Clinton. Other findings in common were hypotension, normal heart size, normal eye grounds, weight loss, nausea and vomiting. A slight or absent response to DOCA and a satisfactory response to salt alone were also striking in these cases. The age of the patient, however, was fifty-three when first seen here. Both patients of Thorn et al. were twenty-one at the time of onset.

Both their patients entered a terminal stage consisting of edema, hypertension, nitrogen retention and cardiac failure. Death in the case presented above was precipitated by acute severe gastrointestinal hemorrhage, the emergency operation and multiple transfusions. Pulmonary edema appeared and was probably responsible for death. This terminal picture was not allowed to develop naturally as in the 2 cases of Thorn et al.

Our case was complicated by the presence of chronic duodenal obstruction. This undoubtedly contributed greatly to the salt loss, particularly the chloride loss. During one period of severe protracted vomiting and hypotension, however, the patient maintained a daily urinary chloride excretion of over 18 gm. (as sodium chloride) and a daily urine volume of over 3 liters. This should have demonstrated that his kidneys were unable to retain chlorides and water at a time when they were most desperately needed to maintain the chemical equilibrium. A similar picture may be seen in adrenal insufficiency when there is moderate salt loss from vomiting, diarrhea, fever or excessive sweating. Here again the kidneys are unable to retain salt in the absence of adrenocortical hormones, the electrolyte balance suffers, and Addisonian crisis may ensue.[5]

The pathological picture of the kidneys in the cases reported by Thorn, Koepf and Clinton[1] could not be called specific. The authors concluded that salt-losing nephritis occurred late in the course of slowly progressive kidney disease. Their cases showed extensive scarring, hypertrophy of the remaining glomeruli, and dilatation of the tubules.[1] The findings in the kidneys in our case were consistent with a severe chronic glomerulonephritis, and nothing that could be interpreted as being a specific tubular lesion was demonstrated.

Instead of atrophy or absence of the adrenal glands, autopsy revealed a fairly marked hyperplasia of the adrenal cortex. It is of interest to note that 1 case of Thorn, Koepf and Clinton also showed definite hypertrophy of the adrenal cortex, although the authors did not comment on this fact. One may speculate that since hypertrophy of the adrenal cortex was present in 2 out of 3 reported cases of salt-losing nephritis the cause of such hypertrophy is the salt loss itself. Such hypertrophy may represent an attempt on the part of the adrenal cortex to stimulate the renal tubules to retain salt and compensate for the excessive salt loss.

It is not known whether a low blood sodium or chloride can stimulate the adrenal cortex.[6] There were undoubtedly other adequate causes for adrenal hypertrophy in this case, but this remains a possibility. A rough parallel might be drawn between such a hypothetical mechanism and the known mechanism of parathyroid hypertrophy in cases in which there is an excessive loss of calcium ion in the urine. Albright et al.[7] have shown that the stimulus to parathyroid hypertrophy in such cases is the depression of blood calcium concentration.

In chronic renal insufficiency significant salt loss is not rare.[8, 9] Its recognition may be very important in cases that show neither edema nor hypertension. When such salt loss exists it contributes to the retention of nitrogenous substances in the blood. The depletion of salt in the body fluids decreases the rate of glomerular filtration probably by reducing the renal blood flow.[10] In such cases the salt loss may be easily replaced by the cautious

addition of extra salt to the diet. This in turn produces a decrease in nitrogen retention. Since the concentration of salt in the urine may be relatively fixed, variation in the urinary volume causes a proportional variation in the total salt excretion. Thus, forcing of fluids may make the salt loss more marked unless additional salt intake compensates for this loss.[8]

Salt loss of sufficient magnitude to cause symptoms simulating adrenocortical insufficiency, however, is probably quite rare.[1] It is important that it be recognized since the response to added sodium chloride and bicarbonate may be quite gratifying. Even with a reasonable suspicion of the presence of such a condition it may be very difficult to rule out the possibility of a combination of both renal and adrenocortical insufficiencies. This can best be illustrated by our experience in the case presented above. Many procedures of use in the diagnosis of Addison's disease were unreliable in the presence of advanced renal insufficiency of this type.

Hypoglycemia is common in Addison's disease and should not be influenced by renal failure. Our patient had no hypoglycemia and had a relatively normal intravenous glucose tolerance test. This indicates that there was no profound disturbance of carbohydrate metabolism and that normal adrenal glands were present.

Urea and creatinine retention decreased by the administration of salt may occur in either adrenal or renal insufficiency. The high degree of retention and its persistence despite vigorous therapy were strong indications that a considerable degree of renal insufficiency was present.

The water diuresis test[2] was positive for Addison's disease in our case. This was to be expected since this test depends on the ability of the kidney to vary the volume of urine and to excrete urea and retain chloride. The functions of the kidney may be impaired in both conditions, and this test was of little or no value in distinguishing this type of renal failure from Addison's disease.[11, 12] A salt-deprivation test[13] might also be expected to yield a positive result in the presence of marked renal salt loss.

Urinary 17-ketosteroid excretion[14] or the urinary output of cortical hormones[15] should be reduced in adrenocortical insufficiency. A low urinary excretion of 17-ketosteroids would have been of little help in itself. This may occur in chronic debilitating diseases even in the presence of anatomically normal adrenal glands.[16] This was true in 1 of the cases of salt-losing nephritis reported by Thorn, Koepf and Clinton.[1] If a normal value had been found in our case it would have been of great help in establishing the proper diagnosis. Unfortunately, laboratory facilities for such assays were not immediately available to us.

Also valuable would have been the determination of eosinophile response to the pituitary adrenocorticotropic hormone.[17] A normal fall in eosinophil count following the administration of this hormone would have been strong evidence for the presence of an intact adrenal cortex. The necessary material, however, was not available to us.

Of prime importance in the establishment of the renal basis for the excessive salt loss in this patient was the lack of a normal response to the administration of DOCA. We observed that large daily doses of the drug did not maintain the patient (Fig. 1) or substantially alter the concentration of chloride in the urine, the blood pressure or the body weight (Fig. 2). Such doses of DOCA should exert a striking effect on the reabsorption of sodium and chloride by the intact renal tubule. In a patient with normal kidneys, with or without normal adrenocortical function, this should manifest itself by a marked reduction in the renal excretion of chloride.[18, 19]

The loss of salt in this type of renal insufficiency may be compared to the more common loss of water. Polyuria, with the excretion of large volumes of urine of low specific gravity, is a frequent symptom of renal insufficiency. This probably represents in part an inability of the renal tubules to reabsorb normal amounts of water. In these respects it resembles the polyuria of diabetes insipidus. Such polyuria, however, is not influenced by the injection of large amounts of the antidiuretic hormone of the pituitary body. It thus represents disease of the end-organ, the renal tubule, simulating disease of the posterior lobe. In salt-losing nephritis the diseased tubule is unable to respond to the influence of DOCA or natural adrenocortical hormones. This again is disease of the same end-organ simulating disease of another endocrine organ — in this case, the adrenal cortex.

Manifestations of the tubular inability to reabsorb water as well as salt were present in our case. Polyuria with the excretion of over 3 liters a day of urine of low specific gravity persisted even during periods of severe dehydration. The specific gravity did not rise after the administration of pituitrin.

This case is presented to point out at least one condition in which *excessive loss* of vital substance in the urine was of primary clinical importance in renal insufficiency. It is more usual to think of renal failure in terms of *retention* of nitrogenous products, electrolytes and water. It is important to recognize the stages of renal insufficiency in which the loss of ability to reabsorb a given solute is significant. The substances that may be lost to an important degree in renal diseases are water, sodium, chloride,[8, 9] calcium,[7] phosphate, amino acids and glucose.[20] Recognition of any such loss makes replacement therapy possible and may lead to the partial rehabilitation of the patient. This was well illustrated by our case, in which compen-

sation for the excessive urinary loss of sodium and chloride led to at least temporary relief from the most pressing symptoms.

Summary

A case of salt-losing nephritis simulating adrenocortical insufficiency, with the pathological findings, is presented.

The difficulties of differential diagnosis and the importance of recognition and proper treatment are discussed.

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TRIMETON, A NEW ANTIHISTAMINIC DRUG*

A Clinical Evaluation

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THOUGH the evidence is still very indirect that histamine is responsible for the allergic reaction,[1, 2] the effectiveness of the antihistaminic drugs in the symptomatic control of hay fever, urticaria and certain cases of perennial allergic rhinitis is well recognized. On the other hand, the value of these drugs in bronchial asthma, allergic dermatoses and drug allergy is questionable. The reason for lack of benefit in these conditions is not clear. The experience with pyribenzamine ointment in the treatment of skin conditions suggests that higher concentrations at the involved site are an important factor. Furthermore, in studies in this laboratory, it has been found that whereas small doses of pyribenzamine injected intravenously may have negligible influence on induced asthmatic attacks,[3] much larger doses often give short-lived protection.[4] These experiments employing larger doses are limited, however, by undesirable side reactions. Also, recent studies have called attention to certain other pharmacologic effects of these drugs,[5] not specifically referable to histamine antagonism. It appears, therefore, that a search for highly specific antihistamines with low toxicity is well warranted. In an effort to obtain these agents, a number of new synthetic compounds have been offered for clinical trial, among which are the substituted pyridyldialkylaminoalkanes. One of these compounds, l-phenyl-1-(2-pyridyl)-3-dimethylaminopropane (trimeton),§ has been shown in animal experiments to possess a high degree of antihistaminic activity and low toxicity.[6, 7] Its structural formula is shown in Figure 1. The purpose of this paper is to report on the efficacy of this drug in certain allergic disorders.

Trimeton tablets for oral administration were given to 84 allergic patients, ranging in age from five to sixty years. These patients, who were about equally divided with respect to sex, had received serial injections of allergenic extracts, and offending allergens had been eliminated so far as possible.

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§Kindly supplied by the Schering Corporation, Bloomfield, New Jersey.

All patients were exhibiting symptoms at the time trimeton therapy was instituted. The drug was given in doses of 25 mg. to 125 mg. a day, and all patients were observed for several weeks and instructed to report in detail all subjective symptoms. In some cases, placebo controls were used. Relief of symptoms, when it occurred, was usually noted thirty minutes after a tablet was taken, and relief often lasted, with certain exceptions, for three or more hours. Withdrawal of the drug was usually followed by a return of the symptoms.

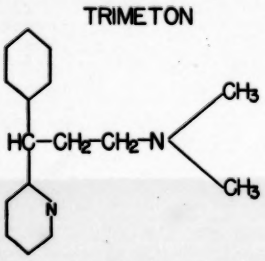

FIGURE 1. *Structural Formula of Trimeton.*

Table 1 presents the results. Twelve patients with urticaria reported satisfactory relief of symptoms. Of 55 patients with perennial allergic rhinitis 47 (85 per cent) reported satisfactory or partial relief. Three of these patients were recorded as having obtained partial relief but actually were benefited satisfactorily for "about half an hour." Increasing the dose of the drug in these cases seemed to make very little difference in prolonging relief. Of 15 patients with hay fever 13 (86 per cent) reported satisfactory or partial relief. One patient with vernal catarrh who had many positive reactions to pollens and a patient with atopic dermatitis failed to obtain symptomatic relief.

TABLE 1. *Therapeutic Response to Trimeton.*

DIAGNOSIS	TOTAL CASES	SATISFACTORY RELIEF	PARTIAL RELIEF	NO RELIEF
		NO. OF CASES	NO. OF CASES	NO. OF CASES
Hay fever	15	10	3	2
Allergic rhinitis, perennial	55	33	14	8
Urticaria	12	12	—	—
Vernal catarrh	1	—	—	1
Atopic dermatitis	1	—	—	1
	—	—	—	—
Totals	84	55	17	12

Of the 84 patients, 74 (88 per cent) were completely free from any undesirable side reactions. The reactions noted in the remaining 10 (11 per cent) were mild, and, in general, could be controlled by a decrease in the dose of the drug. However, in most cases, this resulted in some loss of clinical effectiveness. The side effects were chiefly drowsiness (6 cases, or 7 per cent) and dryness of the mouth (3 cases, or 3 per cent). Nervousness, restlessness, nausea, dizziness or diarrhea was not noted, and weakness occurred in only 1 case (1 per cent).

Discussion

From these limited clinical observations, trimeton appears to be highly satisfactory in the symptomatic treatment of hay fever, urticaria and perennial allergic rhinitis. Trimeton compared favorably with pyribenzamine and benadryl in all respects and is distinctly superior to them in its effect in perennial allergic rhinitis. Experience in this clinic with the latter compounds in the treatment of perennial allergic rhinitis has been disappointing and not in accord with the reports of other investigators. In a number of cases we had the opportunity of prescribing trimeton after pyribenzamine and benadryl had failed to give relief, and frequently trimeton was strikingly effective. In the 55 cases of perennial allergic rhinitis treated with trimeton, there were only 8 (14 per cent) who obtained no relief. Though the number of cases studied was small and treatment with allergenic extracts had been given, the figure of 85 per cent satisfactorily treated patients is impressive.

Trimeton was particularly valuable for its low incidence of side reactions. These were mild and were experienced by only 11 per cent of the patients. Dryness of the mouth and drowsiness were the chief side effects, and such reactions as restlessness, nervousness, nausea and dizziness, found in some of the other commonly employed antihistaminic drugs, were notably absent.

Summary

Trimeton, a new antihistaminic drug, was clinically evaluated in 84 patients with hay fever, urticaria and perennial allergic rhinitis. Because of the favorable therapeutic response, the drug gives promise of being a valuable addition to the growing group of histamine-antagonizing compounds.

Trimeton compares favorably with pyribenzamine and benadryl in the management of certain allergic conditions and appears to be particularly effective in the symptomatic treatment of perennial allergic rhinitis.

The side reactions, occurring in only 10 of 84 patients, were mild.

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MEDICAL PROGRESS

NEUROLOGY

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DURING the past year, significant advances have taken place in many phases of neurology. Increased understanding of the physiology of the cerebral cortex has come from research into the sensory and motor organization of the neopallium of primate brains. New drugs of value in treating myasthenia gravis and states of increased muscular tone have been introduced, and more information concerning the use of antibiotics in treatment of infections of the central nervous system has accumulated. These and other studies are discussed under the following headings: biochemistry, physiology and anatomy; pharmacology; infections; cerebrovascular system; convulsive disorders; myasthenia gravis and familial periodic paralysis; multiple sclerosis; and miscellaneous.

BIOCHEMISTRY, PHYSIOLOGY AND ANATOMY

Woolsey and Hines participated in a symposium on the organization of the primate cerebral cortex, which was held under the sponsorship of the American Physiological Society in 1947. In his discussion at the symposium, Woolsey[1] summarized new work on patterns of sensory representation in the cerebral cortex. Until recently, each of the principal cortical afferent systems was assumed to constitute a main pathway into the cortex, and to be singly represented therein. However, in a series of experiments employing the evoked potential technic, Woolsey has shown that touch, vision and hearing, at least, are doubly represented in each hemisphere.

In her comments on motor organization of the cortex, Hines[1] emphasized that in subhuman primates the frontal lobe has acquired almost complete control of movement. In particular, the anterior division of the precentral motor cortex has assumed the activation of the least stereotyped varieties of extrapyramidal action, and also, that aspect of control of inhibitory action against tone which is unassociated with the pyramidal system. She also pointed out that the posterior division of the precentral motor cortex has a basic organization characterized by localization of both motor activity and inhibitory action against tone. These localized activities are dependent upon the integrity of the corticospinal system. In addition to this discrete organization of skeletal muscle control, there exists, in the same cortical field, a mass organization that survives pyramidal section and is capable of producing not only nonlocalized motor action but also nonlocalized inhibitory action against tone. Both these systems play their part in the control of movements. Under no known experimental conditions can the electric stimulation of extrapyramidal motor fields yield localized contraction of skeletal musculature. Indeed, Hines states, it is the discrete organization of skeletal muscle that distinguished area 4 of the precentral gyrus from all the remaining motor fields of the neopallium of the primate cerebral cortex.

Recent work by Sugar, Chusid and French[2] has afforded further proof that double representation of function in the cortex is not limited to sensation. These workers have described a second motor cortex in the monkey (*Macaca mulatta*), lying on the lateral (exposed) and medial (buried) walls of the frontoparietal operculum, and in the posterior portion of the insula. The arrangement of representation of body parts in this area corresponds roughly to that present in the second sensory cortex of the monkey, which is posterior to this newly described motor area, and slightly overlaps it. The movements elicited from the second cortical motor area were isolated and contralateral.

Evidence that cortical organization is primarily vertical rather than horizontal has been found by Sperry.[3] This investigator crisscrossed the cortex with a knife, penetrating through into the white matter, and found that no impairment of motor function or sensorimotor integration is evident after an interval of a month.

Ward, McCulloch and Magoun[4] have announced that a resting tremor, abolished by movement, has been produced in monkeys by destruction of a small area in the midbrain and pontile tegmentum without injury to the corpus striatum, subthalamus or substantia nigra.

Further evidence for localization in the cerebellum has been introduced. Nims and Nulsen[5] have found that in cats each muscular contraction elicited from the cerebral cortex can be inhibited by stimulation of a topical area of the cerebellum with precise localization.

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In an important monograph recently published, Lorente de Nó[6] has detailed the results of a decade of research into the physiology of nerve. It is impossible to summarize the many contributions described in his monograph, which will be consulted by everyone interested in this field of investigation. Among other findings, Lorente de Nó has adduced evidence that the membrane potential of a resting nerve is maintained by some component of its oxidative metabolism, rather than by diffusion potentials or Donnan equilibriums resulting from the distribution of cations and anions across the cell membrane.

Hydén[7] has described the results of cytochemical experiments on nerve cells in which the ultraviolet spectrophotometric technics developed in Caspersson's laboratory were utilized. Nucleotides and certain proteins have convenient absorption ranges for study with these procedures. Hydén has found that, in the course of intense muscular work, there is a sharp decrease in the content of protein and nucleic acids in the cytoplasm of anterior-horn cells. Acoustic stimulation of guinea pigs with tones of various frequencies and intensities produces extensive cytochemical changes in the nerve cells of the cochlear ganglion. After exposure to a tone of a frequency of 6000 cycles per second, and intensity of 80 decibels, for three hours, the ganglion cells pass through a cycle of changes, with decreases in nucleotide and protein concentrations, which reach a maximum in the second week after stimulation. Concentration levels of protein and nucleotide are restored to those of nonstimulated controls within the third week after stimulation. Electroaudiogram studies done on the stimulated animals showed no decrease of auditory functions below those of nonstimulated animals, in the period after stimulation during which cochlear ganglion-cell protein and nucleotide concentrations were decreased.

Hydén[7] has also found that the neurones of patients suffering from long-standing manic-depressive and schizophrenic psychoses have lower protein and nucleotide contents than those of controls. Treatment of patients with these psychoses by means of malonitrile, considered a precursor of certain nucleotides, is reported to produce varying degrees of beneficial psychic stimulation. It is understood that certain issues involved in these observations on psychotic patients are not yet entirely clarified.

De Robertis and Schmitt[8] have described the presence of tubular structures in invertebrate and vertebrate nerve preparations studied with the electron microscope. They consider these to be located intraneuronally and to be of possible significance in neural conduction.

A change in the quality of pain sensation is present in a number of clinical conditions in which there has been injury to, or disease of, the central or peripheral nervous system. In a study of the anatomic basis for alterations in quality of pain sensibility, Weddell and his collaborators[9] have studied the histologic appearance of areas of skin in the territory of recovering nerve lesions, and of scar tissue from cutaneous scars, in a total of 59 patients, and have correlated their anatomic findings with the results of sensory stimulation. They found that in every case in which an unusually unpleasant quality of pain could be elicited by means of a needle prick, the underlying nerve terminals subserving pain were isolated from their neighbors and no overlapping of terminals was present. Conversely, in no case in which this isolation was not found microscopically, could pain of unpleasant quality be produced. It was also found that alterations in the quality of pain sensibility were not correlated with the presence of morphologically abnormal pain endings. Such endings, however, were associated with disturbances of the threshold of pain sensibility.

This pattern of innervation found in areas of abnormal sensation offers marked contrast with that of normal skin, which has been extensively investigated by Weddell.[10] He has found that in normal skin the network of nerve endings subserving the sensation of pain is disposed in such a manner that any one area of skin is supplied by several overlapping terminals derived from different axons.

Thus, these investigators conclude that the occurrence of "over-reaction" to painful stimuli in various clinical conditions is caused by a "reduction in the normal pattern of impulses presented to consciousness," and present the hypothesis that abnormal sensation of pain in association with central disturbances — for example, in the "thalamic syndrome" — is associated with a "reduction in pattern" through damage to particular central nervous pathways.

Feindel et al.[11] have introduced the use of methylene blue injected into an experimental subject before death as a method of staining nervous tissues in vivo.

Pharmacology

In the course of an investigation into the pharmacology of glycerol ethers, Berger and Bradley[12] made the observation that α:beta-dihydroxy-gamma-(2-methylphenoxy)-propane, subsequently named "myanesin," causes a transient relaxation and paralysis of certain skeletal muscles in dosages that do not affect the diaphragm and intercostal muscles, blood pressure or state of consciousness. This drug has been taken up quickly by clinicians, and is reported as useful in producing relaxation during light anesthesia,[13] in spastic conditions,[12] in diminishing parkinsonian tremor and thalamic pain states[14] and in halting jacksonian seizures.[15]

Early reports on myanesin[15] stressed the fact that limitations to usefulness of the drug lie in its inefficacy after oral administration and in its evanescent action intravenously. However, a recent report by Berger and Schwartz[16] maintains that in proper dosages and preparations the drug is effective orally in many patients, and that a more or less constant action can be achieved by repeated administrations. These investigators give myanesin in a 3.3 per cent (weight in volume) solution in 20 per cent (volume in volume) aqueous propylene glycol, with syrup of cherry 20 per cent (volume in volume) to improve taste of the mixture. The usual dose employed by Berger and Schwartz is 30 cc. of this mixture, which contains 1 gm. of myanesin. The medication is repeated as necessary; in some cases Berger and Schwartz have given it as many as five times daily. Although myanesin apparently has a low toxicity and wide margin of safety,[12] the drug is not without serious side effects. One death has been attributed to the compound.[17] Wilson and Gordon[18] report that red-cell fragility is increased, and that there is demonstrable hemolysis in the blood stream of children given myanesin intravenously. On the other hand, Berger and Schwartz[16] state that after oral administration there is no hemolysis. However, they warn of the possibility of as yet undemonstrated toxic effects of myanesin in patients who receive the drug over a long period.

The mode of action of myanesin is not yet clear. Stephen and Chandy[14] have reported that the drug has no action on the transmission of nervous impulses along nerve trunks, across myoneural junctions or on synapses involved in spinal reflexes. Mallinson[13] has pointed out that it differs in its mode of action from that of curare not only in an absence of effect on myoneural junctures but also in inducing relaxation of abdominal muscles without concomitant intercostal paralysis. Hunter and Waterfall[15] have stated that myanesin when given into an antecubital vein to several patients stopped jacksonian seizures in thirty seconds, an interval slightly in excess of the time they have established as arm-brain circulation time. They consider this to be presumptive evidence for a central action of myanesin, in view of Stephen and Chandy's[14] demonstration of the absence of a more peripheral effect.

Parpanit, a drug employed in Europe in the production of relaxation of skeletal muscle, has been reported as not acting through the myoneural juncture.[19]

Telfer[20] has stated that the use of BAL in lead poisoning gives encouraging results, and reports of its use in arsenical intoxications have appeared.[21]

Wollenberger[22] has reported that the cardiac glycoside ouabain, in low concentrations, increases the oxygen uptake of guinea-pig cortex slices, in the presence of glucose, pyruvate or lactate. In higher concentrations, an initial increase of respiration of the cortical slices is followed by a depression. However, Wollenberger found that the glycoside has no effect on the respiratory activity of homogenized brain tissue or of isolated oxidative enzymes. He has concluded that ouabain does not directly affect the catalytic function of respiratory enzymes, but that its influence on respiration of brain slices is dependent upon the integrity of cellular structures, the site of action of the drug presumably being at the cell surface. The increase in cell respiration is perhaps due, at least partially, to facilitation of entry of exogenous substrate into the cell, the subsequent depression of respiration resulting from the loss of one or more diffusible respiration catalysts.

In connection with Wollenberger's observations, it is interesting to note that Gold et al.[23] have reported that ouabain, as well as several other digitalis glycosides, produces convulsions in rats.

Cerebrovascular System

A complete report by Kety and Schmidt[24] has appeared on the nitrous oxide method for quantitative determination of cerebral blood flow in man. This procedure is based on determination of the rate at which nitrous oxide breathed in a gaseous mixture at low concentration equilibrates with brain tissue. This equilibration occurs within ten minutes, and from a mathematical analysis of the curves of nitrous oxide concentration in arterial and venous blood during this period, and the use of Fick's principle, the cerebral blood flow can be obtained. Kety and Schmidt have checked their method by direct measurement in the monkey with a bubble flow meter, and by a comparison of the brain concentration of nitrous oxide with blood concentration at equilibrium. In 14 healthy young men, cerebral blood flow was 54 cc. per minute per 100 gm. of brain tissue, with a deviation of plus or minus 12 cc. per minute. A mean value of cerebral oxygen consumption was found to be 3.3 cc. per 100 gm. of brain tissue per minute, with a deviation of plus or minus 0.4 cc By the use of this procedure, Kety and Schmidt[25] studied the effect of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow. Increased arterial carbon dioxide tension produced an increase in cerebral blood flow averaging 75 per cent. High oxygen tensions were associated with a reduction in cerebral blood flow of 13 per cent, whereas anoxemia was associated with an increase of 35 per cent in flow. Measurement of cerebral oxygen consumption showed that no changes occurred in this metabolic activity as a result of changes in arterial tensions of oxygen and carbon dioxide producing the changes in blood flow described.

In a further study, Kety, Shenkin and Schmidt[26] studied the relations between cerebral circulation and

intracranial pressure. In 12 patients with brain tumors, the rise in cerebrospinal-fluid pressure produced by the brain tumor was associated with a progressive increase in mean arterial blood pressure and cerebrovascular resistance and, above a critical level of cerebrospinal-fluid pressure equivalent to about 450 mm. of water, with a definite decrease in cerebral blood flow. In this group of patients with increased intracranial pressure, a good correlation between state of consciousness and cerebral oxygen consumption was found. The conscious patients yielded a mean value for cerebral oxygen consumption of 3.1 cc. per 100 gm. of brain tissue per minute, whereas the comatose group averaged 2.5 cc. per 100 gm. per minute, the average in normals being 3.3 cc. per 100 gm. per minute. Similarly, the patients with cerebral blood flow below 40 cc. per 100 gm. per minute were all comatose.

An interesting study of the physiology of the circle of Willis has been carried out by Rogers.[27] Since the time of Willis, who introduced the concept, many have considered that his structure acts as a reservoir, or distributor station, serving equally all vessels leading from it and, consequently, equalizing cerebral blood flow. Alternatively, the circle may be conceived as acting merely as an anastomosis, with the potentiality of opening up should a major vessel supplying it be occluded. Rogers reports on the anatomy of the structure, injection studies in cadavers, cerebral arteriography in the living and the behavior of a working scale model. Anatomically, he has found that the circle of Willis is almost always a closed ring, but that considerable variation occurs in the size of component vessels. Injections of methylene blue kept the dye for the most part in the postcircle distribution of the artery, which was injected proximal to the circle. In patients on whom cerebral arteriography was done, injections into the carotid arteries on one side was followed by distribution of the injection mass mostly into the middle and anterior cerebral arteries on the side of the injection. The working model of the circle of Willis constructed by Rogers gave results in injection experiments similar to those described on cadavers. Rogers states that the result of carotid ligation is a reduction of flow in aneurysms of vessels distal to the circle on the side of the ligation, concluding that these findings support the idea that the circle of Willis works as an anastomosis, and not as a reservoir.

Although cerebral hemorrhage commonly takes the form of massive intracapsular bleeding in an arteriosclerotic subject in the older age group, less frequently hemorrhage occurs elsewhere in the brain in a young and apparently healthy person. Jewesbury[28] has discussed the etiology, clinical picture and treatment of the latter group. He points out that small intracerebral aneurysms, angiomas and other vascular anomalies have rather frequently been identified as the source of the hemorrhage. Less frequently, eclampsia, polyarteritis nodosa, mycotic aneurysm and cerebral tumor are the basis of hemorrhage. He states that head injury, even when apparently slight, is an important etiologic factor, and may produce immediate or delayed effects. There are a number of cases in which no adequate explanation of the bleeding can be given. In the majority of these patients the clinical picture is that of a slowly expanding intracerebral lesion, and not one of sudden apoplexy. This kind of clinical picture results from the development of a subcortical hematoma, which tends to become encysted and to increase slowly in size. Jewesbury reports a number of cases of this type that have responded well to evacuation of the cyst by surgical intervention.

Krainer[29] has reported 7 fatal cases of cerebral thrombosis in young Indian adults, 3 of which were due to thrombosis of infected cerebral arteries. Two of the patients had syphilis, 1 had cerebral malaria, and 1 had thrombosis in association with a spontaneous aneurysm. Three cases were caused by thrombosis of infected cerebral arteries, which were thought to be due to transpulmonary embolism of infective particles, from foci in the systemic circulation.

One hundred and thirty patients with subarachnoid hemorrhage have been analyzed by Hamby.[30] Forty-four of 47 proved cases were caused by ruptured aneurysms. In 23 of 44 fatal cases, intracerebral hematomas were present. Of the 130 patients, 67 died in the hospital. A follow-up report on 62 of the 63 patients who left the hospital shows that 17 have died. Of the 45 living patients, 21 have recovered completely, 13 are able to work despite neurologic handicaps, and 11 are invalids. Hamby reports that unfavorable prognostic features are: previous attacks, recurrent episodes of bleeding while the patient is in the hospital, and the presence of mental disturbances, unconsciousness and convulsions.

Wechsler and Gross[31] have described the usefulness of cerebral arteriography as both a diagnostic and a therapeutic guide in patients with spontaneous and subarachnoid hemorrhages. Subarachnoid hemorrhage was associated with a vascular anomaly in 6 of 10 cases reported, and with an aneurysm in 4.

Gilbert and de Takats[32] reported on the results of blocking of the cervical sympathetic trunk with procaine on the side of the lesions in 25 patients with apoplexy. A transient improvement was noted in 19 patients, manifested by a return of consciousness and of speech, and enhanced motor performance. The authors suggest that this procedure, along with other means of combating cerebral edema and stasis, is of value in the treatment of apoplexy.

Sindell[32] has stated that 3 patients, in hypoglycemic coma during insulin shock therapy, were brought out of coma by the administration of either amyl nitrite or nicotinic acid, or both. He suggests that the use of vasodilators is valuable in the treatment of patients with apparently irreversible hypoglycemic coma.

The cold-pressor reaction has been studied in psychotic patients with cerebrovascular disease by Becker and his co-workers.[34] They report evidence that there is an increased response to the vasopressor test in such patients. Persons with well advanced cerebral arteriosclerosis showed the most marked response.

Zeman and Siegal[35] have described the development of a permanent paralysis of the right arm in an eighty-three-year-old man with long-standing hypertension following massage, alternately, of the carotid sinuses. They state that 8 cases of irreversible cerebral changes, occurring after carotid-sinus pressure, have been reported in the literature. These accidents have taken place, usually, in elderly patients.

A study of hypertensive encephalopathy has been made by Pickering.[36] He divided this condition into two distinct forms. In the first form, acute hypertension, or chronic hypertension with an acute exacerbation of hypertension, may be associated with headaches, vomiting, convulsions and coma, as the result of acute edema of the brain. Pickering explains these symptoms on the basis of "defective constriction" of cerebral vessels with the increased intravascular pressure, which is present in association with the hypertension, leading to an outflow of fluid into the brain. In the second form, which is associated with chronic hypertension, Pickering thinks attacks of local motor or sensory paralysis are the result of sudden arterial occlusion of larger or smaller vessels, caused, perhaps, by a thrombus. He attributes the phenomena of hypertensive encephalopathy to mechanisms other than arterial spasm for several reasons. He points out that cerebral vessels have poor musculature, and that they constrict feebly in response to known vasoconstrictor agents. Also, in many of his patients with chronic hypertension, Pickering was unable to draw a sharp dividing line between bouts of paralysis lasting for a short while, and those lasting permanently, which he regards as an argument against vasospasm as the cause of the symptomatology.

Myasthenia Gravis and Familial Periodic Paralysis

Approximately 200 patients with myasthenia gravis have undergone thymectomy as treatment for their disease. Harvey[37] has pointed out that 15 per cent of these patients show marked improvement, and has commented that an analysis of why the operation failed to result in marked improvement in the other 85 per cent should be of value in understanding the disease. In discussing the results of thymectomies done at Johns Hopkins Hospital, he states that the two factors most favorable for good response to the procedure are performance of the operation early in the course of the disease and prior administration of only small amounts of neostigmine. Harvey states that it is not necessary for a thymoma to be present for a remission to occur after thymectomy, since some patients whose thymus glands show only moderate hyperplasia also improve. Incidentally, a thymoma, if present, may not be demonstrable by x-ray examination. Histologically, the tumors removed at Johns Hopkins Hospital have shown varying amounts of neoplastic tissue, which arises from epithelial cells of the thymus reticulum; lymphocytic hyperplasia is also present. Patients who have shown a response to thymectomy manifested improvement of strength predominantly in their limb and trunk muscles, with less increase of power in muscles supplied by cranial nerves.

Tetra-ethylpyrophosphate (TEPP), a drug with a powerful anticholinesterase activity, has been introduced recently by Burgen and his colleagues[38] for the treatment of myasthenia gravis, and promises to be of considerable value. This drug, whose actions are reported to resemble those of eserine and neostigmine more closely than those of diisopropyl fluorophosphate (DFP), is as potent as eserine and a third as potent as neostigmine in tests on rats. The duration of its action, however, is twenty-four to forty-eight hours, in contrast with the two to three hours that is the period of action of eserine and neostigmine. TEPP is well absorbed when given by mouth.

When given orally to 3 patients with myasthenia, TEPP was found to be a completely effective substitute for neostigmine, and, because of its longer action, its effect was much smoother than that of neostigmine. Burgen et al.[38] state that they have found 10 mg. of TEPP given by mouth to be as effective as oral doses of 100 to 150 mg. of neostigmine. The maintenance dose of TEPP varies from 8 to 12 mg. daily, administered orally in two or three doses.

The side actions of TEPP consist in visceral and central effects similar to those of neostigmine. The most pronounced side action is on the gastrointestinal tract, colic and diarrhea being produced. This visceral action is prevented effectively by atropine. The central side effects, produced in all of Burgen's patients during dose stabilization, included vertigo and nystagmus. Nausea and vomiting, sweating and pallor also occur. The last two groups of effects were not prevented by atropine.

Grob and his associates[39-41] have summarized their extensive clinical research with diisopropyl fluorophosphate (DFP). They find that whereas administration of DFP to patients with myasthenia

gravis results in considerable gain in strength, in no case was the improvement as great as that obtained with neostigmine, and they believe that the unpleasant central nervous and gastrointestinal symptoms produced by DFP preclude its use in amounts sufficient to produce therapeutic effects. They have found evidence that DFP and neostigmine compete for cholinesterase (Ch-E) and that formation of a neostigmine-Ch-E complex prevents irreversible inhibition of Ch-E by subsequently injected DFP, thereby blocking the effect of DFP.

Torda and Wolff[42] have reported that injections of a mixture of essential amino acids effect an increase in strength of patients with myasthenia, presumably through influencing acetylcholine synthesis.

In familial periodic paralysis, the close association of a fall in concentration of serum potassium with the onset of muscular paralysis and the relief of muscle weakness that ensues after administration of potassium salts are both well known and indicate that a defect in potassium metabolism is involved in the pathological physiology of this disease. The nature of the disorder of potassium metabolism is not understood, however.

Danowski et al.[43] have studied, in a quantitative manner, the exchange of potassium and sodium between the extracellular and intracellular phases of the body fluids in 2 patients with this disease. They found that during the development of paralysis, potassium shifted from the extracellular to the intracellular phase, with a resultant sharp decline in serum potassium concentrations. During recovery, large amounts of administered potassium were taken up by the intracellular phase before extracellular loss was replenished. Reciprocal transfer of sodium was observed in one patient, but not in the other. No significant changes occurred in the volume of total body water and extracellular fluid, and there was no increase in potassium excretion in urine or feces.

Gass et al.,[44] in a study of a patient with familial periodic paralysis by means of radioactive potassium, were unable to detect, with a surface Geiger counter, any increase in radioactivity over either muscles or liver in an induced attack of paralysis. Nor could they find a shift of potassium into spinal fluid or red cells. Thus, although from the study of Danowski and his co-workers[43] it appears clear that during an attack of paralysis potassium moves into the intracellular phase of the body fluid of the patient, and is not excreted in the urine or feces, on the basis of Gass's work it is not possible to determine into which particular organ or cellular system the potassium migrates. It should be pointed out that there are certain equivocal aspects to the observations of the latter investigators, and further studies with tracer or other appropriate technics may well show that the potassium moves into the muscle at the onset of paralysis.

Multiple Sclerosis

Although previous reports have described the production of such lesions in monkeys by similar methods, the production of disseminated encephalomyelitis in rabbits by the injection of homologous spinal-cord homogenates with adjuvants has now been reported by Morrison.[45]

Langworthy[46] has discussed a number of patients suffering from multiple sclerosis who showed signs of conversion hysteria either before or after the development of signs of organic disease. These patients also manifested pronounced evidences of vasomotor instability in their extremities, and Langworthy asks whether vascular changes in the brain related to neurotic difficulties may not lead in turn to organic disease. Langworthy believes that psychotherapy offers as hopeful an approach to the therapy of multiple sclerosis as any other treatment now available.

Eighteen patients with multiple sclerosis who showed constrictions of retinal arterioles have been reported by Franklin and Brickner.[47] In one of their patients, constriction was seen in a retinal venule. Frequently, scotomas and, occasionally, a reduction in visual acuity, associated with the arteriolar constriction, were also present. The objective findings are stated to have coincided with the subjective complaints of the patients. In most cases in which they were employed, fast acting, vasodilating drugs such as amyl nitrite, administered by inhalation, caused prompt, temporary relaxation of the arteriolar constrictions and, concomitantly, a reduction in the size of the scotoma. In several cases, an increase of visual acuity was noted in patients in whom a reduction of acuity was associated with arteriolar constriction. Franklin and Brickner regard the constrictions as spasms of arterioles, and they develop the hypothesis that the lesions throughout the central nervous system in multiple sclerosis are caused by diminution of the blood supply to neural tissue resulting from vasospasm.

In an investigation of the loss of axis cylinders in sclerotic plaques by means of the Bodian silver stain, Putnam and Alexander[48] state that some degree of damage or destruction of axons occurred in all the sclerotic plaques investigated. Similar changes of a corresponding degree of intensity were seen in other central-nervous-system lesions of vascular origin.

Epilepsy

Himwich and his colleagues[49] have described the appearance of high-amplitude waves of grand-mal type in the electroencephalogram of rabbits after the injection of di-isopropyl fluorophosphate into a carotid artery. The high-amplitude waves appear first in the cortex on the injected side, subsequently spread to the opposite cortex and are maintained for an hour. Di-isopropyl fluorophos-

phate effects an irreversible inhibition of cholinesterase, the enzyme that hydrolyzes acetylcholine, and thus produces an accumulation of acetylcholine. These workers have correlated their findings with the recent evidence indicating that certain kinds of convulsions are related to abnormalities of acetylcholine metabolism. It is interesting to compare this study with that of Pope et al.,[50] who have shown that in trigger areas of the cortex of animals with experimentally induced focal epilepsy, there is an increase in cholinesterase concentration.

The results of a decade of systematic investigation into the anticonvulsant action of many classes of compounds have been summarized by Merritt and Brenner.[51] Over 700 compounds were first investigated for their action in protection of cats against electrically induced convulsions. About 10 per cent of the 700 compounds were found to produce a significant elevation of the convulsive threshold in acute experiments.

Classes of compounds found to possess activity in raising electrical threshold include barbiturates, benzoazoles, hydantoinates, ketones, oxazolidinediones and phenyl compounds containing sulfur. So far only a few of these compounds have been tested clinically. Of those tested, 5,5 diphenylhydantoin (dilantin) has proved to be the most effective anticonvulsant yet discovered. Of possible equal or greater value is 5 methyl, 5 phenyl hydantoin. The latter compound is not suitable for general use because of its toxicity.

Ellermann[52] has reported on the use of 5,5-diphenyl-2,4-dioxazolidinedione (epidon) in epilepsy. Apparently, on the basis of records of patients presented, the drug when administered in dosages of 2 or 3 gm. daily is effective in controlling grand-mal and psychomotor seizures. It is not possible from the cases quoted in Ellermann's article to compare the effectiveness of epidon with that of other anticonvulsants such as dilantin, since the patients described were not receiving adequate dilantin therapy at the time they were started on epidon. Ellermann states that toxic reactions with epidon were a fifth as frequent as those with dilantin.

As an assay of the efficacy of anticonvulsants, the activity of various drugs in preventing the tonic phase of electroshock in nonepileptic subjects has been introduced by Toman et al.[53]

Another fatal case of acute pancytopenia following tridione therapy has been reported.[54] This brings the total of reported deaths to 3. In a careful and convincing study, Barnett, Simons and Wells[55] have described a patient who on three occasions developed a nephrotic syndrome following administration of tridione. These reports emphasize the necessity of repeated blood and urine examination in patients receiving this substance.

Russell[56] has employed a technic of correlating the areas of cortex involved in head wounds with the incidence of post-traumatic epilepsy in patients who have received head wounds. Although casual inspection of the cortical maps presented impresses one with a predominance of involvement in the "suppressor" areas of cortex in patients who develop traumatic epilepsy, R. A. Fisher has analyzed the maps and has concluded that there is no statistically significant difference in location of wounds in the two groups of patients.

Recent work by Elvehjem and his colleagues[57] at Wisconsin, on the production of running fits in dogs by white flour bleached by the "agene" process wth nitrogen trichloride, has aroused interest in the possible role of flour so manufactured in epilepsy in human beings. However, that there is a species difference in the effect of the "agenized flour" is illustrated by the fact that although feeding of this substance to cats and dogs produced fits, monkeys so treated did not develop them but did show some changes in their electroencephalograms, and that 12 human beings fed highly agenized products for two to four weeks did not show either convulsions or electroencephalographic changes.[57] The fraction of flour showing the toxic factor has been demonstrated to be the wheat protein, and not the lipid or carbohydrate fraction. Of course, epilepsy in its form known today in human patients plagued man long before "agenized" flour was ever manufactured.

Abbott and Schwab,[58] in analyzing patients with epilepsy showing normal electroencephalograms between seizures, point out that such patients have a better prognosis with respect to frequency of future spell, response to medicine, likelihood of remissions while off medication and capacity for work, than those with abnormal records between convulsions. Their patients with abnormal interseizure patterns usually had had convulsions in childhood, or had suffered brain injuries.

Infections

Reports on the efficacy of penicillin in the treatment of neurosyphilis continue to appear.[59-64] Thus, Dattner and his co-workers[59] report satisfactory results in 151 patients with both asymptomatic and symptomatic neurosyphilis. They employ 40,000 units of penicillin given intramuscularly every three hours for 150 doses, a total of 6,000,000 units; 90 per cent of their patients gave satisfactory responses. and these investigators believe that penicillin is as effective as and will eventually replace fever therapy.

Heyman,[60] however, recommends penicillin for asymptomatic and early symptomatic syphilis, but believes that fever therapy should be used in treating late symptomatic neurosyphilis.

Isolated cases of the apparent cure of tuberculous meningitis have been reported. Mehas and Truax[65]

have described a thirty-one-year-old woman with proved tuberculous meningitis in whom intramuscular and intrathecal streptomycin apparently arrested the progress of the disease. Appelbaum and Halkin[66] report the case of a nine-year-old boy with tuberculous meningitis and pulmonary miliary tuberculosis whose disease was completely arrested by intrathecal and intramuscular administration of streptomycin. Although in the former patient residual damage to the central nervous system was present, in the latter there were no neurologic residua.

Now that there is a hopeful therapeutic procedure for this previously incurable malady, the necessity of early diagnosis of tuberculous meningitis increases. This is especially true since the chance of avoiding serious, permanent, neurologic sequelae probably depends on early institution of therapy.[67] Tuberculous meningitis is commonest in the first decade of life, and therefore it is in young children that particular watch must be kept for early signs. It has been emphasized[67] that the presenting features of tuberculosis of the meninges are many and varied, but that most cases conform to a general pattern of symptomatology. Most often the meningitis begins insidiously, with symptoms mimicking minor ailments. Rarely, the onset of tuberculous meningitis is sudden, with focal signs in the nervous system, such as cranial-nerve palsies, limb paralyses and focal and generalized convulsions. Headache, fever and stiff neck are frequently present. Demonstration of a low and falling spinal-fluid sugar value is of great diagnostic help in early stages.

Paine et al.[68] have described the use of streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system. Two patients with *Pseudomonas aeruginosa* infection, 2 with Type B *Haemophilus influenzae* infections, and 1 patient with *Proteus vulgaris* infection all recovered after treatment with streptomycin. Streptomycin was given intrathecally in doses of 0.05 gm. in 1 cc. of sterile physiologic saline solutions daily. Concomitantly, streptomycin was administered intramuscularly in doses varying from 0.02 gm. to 4 gm. every six hours. The fact that fever may rise during streptomycin therapy, as a result of drug toxicity, makes it difficult to decide at what point treatment should be terminated. Frequent cultures of the spinal fluid are a helpful guide in making this decision.

Hoyne and Brown[69] have reported a series of 30 patients with type B *H. influenzae* meningitis, 28 of whom recovered after treatment with various combinations of specific serum, sulfonamides and streptomycin. They emphasize particularly that 23 of the 28 patients who recovered received no intrathecal therapy.

Accounts of the involvement of the nervous system in trichiniasis have recently appeared. MacAndrew and Davis[70] have reported the case of a thirty-nine-year-old woman with trichiniasis whose presenting symptoms were right footdrop and right-facial-muscle palsy. These writers point out the importance of consideration of this disease in diagnosis of patients with unexplained neuritis. Skinner[71] has described 2 cases of depression and delirium in which trichiniasis was present. The clinical condition of 1 of the patients resembled delirium tremens.

Collard and Kendall[72] have presented the case of a patient with cerebral amebiasis whom they successfully treated with emetine. The authors state that this patient is the first reported in the literature who has recovered from amebiasis of the central nervous system. This condition has had a fatal outcome even after therapy with emetine or evacuation of amebic cerebral abscesses neurosurgically in all patients heretofore reported. Collard and Kendall attribute the recovery of their patient to early institution of treatment, probably at a stage of focal amebic encephalitis, before actual abscess formation had occurred.

A comprehensive report on involvement of the nervous system in schistosomiasis has been made by Kane and Most,[73] who point out that the three species of schistosoma demonstrate predilections for localizing in different parts of the central nervous system. Thus, *S. japonica* invades the brain, whereas *S. mansoni* and *S. haematobium* go invariably to the spinal cord. Correspondingly, the symptomatology varies, *S. japonica* manifesting itself by diffuse encephalitic symptoms, focal paralyses, epileptic seizures or signs of an expanding intracranial lesion. On the other hand, *S. mansoni* and *S. haematobium* produce signs of myelitis or spinal-cord compression. The authors emphasize the fact that the diagnosis of this condition should be considered in any patient with these findings who has been exposed to possibly infected fresh water in any one of the endemic areas in the South Pacific Area (Japan, Formosa, China and the Philippines). It may be as long as four years after infection before central-nervous-system involvement is manifested. The treatment described by Kane and Most consisted usually in administration of antimony potassium tartrate, accompanied, if the clinical condition made it necessary, by appropriate surgical intervention. Prognosis is usually good for arrest of the disease, but, of course, neural tissue destroyed before treatment is instituted will not be restored.

A patient with a large granulomatous tumor in the right occipitoparietal region of the brain, caused by infestation with *S. japonica*, has been described by Reeves and Kerr.[74] The preoperative diagnosis was an expanding intracranial lesion, and the possibility of its being on the basis of schistosomiasis was not seriously considered, since no historical or clinical evidence pointed to the parasite, except for exposure in the endemic areas of Leyte and Mindoro.

The clinical characteristics of an epidemic of Japanese B encephalitis occurring as an outbreak in the civilian population of Okinawa have been reported by Lewis et al.[75] Among 63 patients, most of whom were children, the mortality was approximately 20 per cent. The clinical manifestations were characteristic of a diffuse encephalomyelitis and resembled those of other neurotropic virus infections. Permanent disorders of the nervous system of variable degree resulted in a fifth of the patients. A postencephalitic parkinsonian syndrome occurred rarely. It was found that accurate diagnosis depended upon the use of specific serologic and virologic tests.

Gibbs and Gibbs[76] have analyzed the electroencephalographic findings in 240 cases of encephalitis in various stages of the disease. They state that the abnormalities are often focal and can be correlated with the stage of the disease. During the acute and subacute phases the electroencephalographic findings correlate with the general severity of symptoms. However, the only feature of the postencephalitic syndrome that correlates highly with electroencephalographic abnormality is the presence of convulsions. The electroencephalogram has diagnostic value for encephalitis, and after the acute phase is past it has prognostic value for postencephalitic epilepsy. Wave and spike activity of the petit-mal type is a common sequel of encephalitis in children.

Hoyne and Schultz[77] have reported the case of a patient who had five attacks of meningitis in five years, four of them resulting from a pneumococcus, and the fifth from *H. influenzae*. At autopsy, two small, inexplicable perforations were found behind the crista galli that led into the ethmoid cells and nasopharynx. The authors suggest that every patient with pneumococcal meningitis have skull x-ray films taken with special reference to the sinuses.

Miscellaneous Considerations

Neuropathological aspects of thrombocytic acroangiothrombosis have been detailed by Adams, Cammermeyer and Fitzgerald.[78] This name is applied to a rare disease, of which 13 cases are described in the literature. The etiology is unknown. The disease is characterized by fever, malaise and cerebral symptoms ranging from muscular weakness, hemiplegia, convulsions and confusion to coma. Hematologically, an anemia and thrombopenia are present. The disease runs a rapidly progressive course, death ensuing in from a few days to eight weeks. Neuropathologically, platelet thrombi are found in cerebral vessels, sometimes associated with multiple small foci of parenchymal necrosis and pectechial hemorrhages. A clinicoanatomic correlation of neurologic symptoms is usually not possible. This condition must be distinguished clinically from idiopathic thrombopenic purpura, lupus erythematosus, subacute bacterial endocarditis and rickettsial infections. The differentiation may be possibie on the basis of the total clinical picture and laboratory data. The diagnosis could probably also be established by bone-marrow autopsy, since platelet thrombi and vascular hyperplasia are often observable in the bone marrow.

Bethell and Sturgis[79] have described 70 cases of pernicious anemia studied over periods of not less than ten years. Most of the patients, whether treated with oral preparations of stomach or liver, or parenteral crude or refined liver extracts, showed significant improvement in their neurologic manifestations. The period of improvement was limited essentially to the first year of therapy. Thirty-six patients who had regular therapy and complete hematologic remission afforded no case of development or progression of neurologic symptoms; 15 patients who did not adhere to optimal therapy, and who had abnormal blood values, showed transient and reversible neurologic manifestations, which cleared up on resumption of therapy, and 19 patients who suffered clinical and hematologic relapses manifested only rarely serious progression of neurologic disease. However, the authors point out that these results do not justify the conclusion that irregular or suboptimal therapy of pernicious anemia is without serious possibilities.

Ross and his collaborators,[80] reporting on the use of folic acid in the treatment of pernicious anemia, state that 11 of their patients developed, or showed progression of, subacute combined degeneration of the spinal cord during folic acid therapy. Neurologic involvement developed in most of these patients when the peripheral blood was normal. The institution of liver-extract therapy, in addition to folic acid maintenance therapy, failed to prevent progression of the disease in 4 patients, and only partially arrested the disease in the fifth, in whom, indeed, improvement occurred more rapidly when folic acid was discontinued. In the experience of these physicians, subacute combined degeneration of the spinal cord occurred with greater frequency in patients on large daily doses of folic acid than it did in patients with small or intermittent doses. They suggest that folic acid in large daily doses may actually precipitate or aggravate neurologic disease.

Friedman and Brenner[81] report that the intravenous injection of 100 mg. of sodium nicotinate did not produce relief of pain in any of 7 patients suffering from acute migraine attacks. These investigators did not find this compound to be any more effective in the symptomatic relief of patients with psychogenic or post-traumatic headache than physiologic solution of sodium chloride injected intravenously in small amounts.

Mills[82] has reported that potassium thiocyanate is of some value in the relief of headaches suffered by patients with benign and malignant hyperten-

sion. Symptomatic relief resulted in patients in whom no fall of blood pressure was noted. Administration of thiocyanate afforded no relief of headache in patients with malignant hypertension whose blood urea nitrogen was elevated.

Dow and Whitty[83] have made an electroencephalographic study of 51 patients with migraine headaches. Generalized dysrhythmia was observed in 14, symmetrical, bilateral, episodic, abnormal activity in 12, and a persistent abnormality in 4. Exaggeration of a previous abnormality was noted at the period of aura in 5 of 8 cases, and after ergotamine tartrate administration in 3 of 5 cases. The transient focal abnormality described by Engel et al.[84] was not observed.

A simple classification of headaches has been suggested by Butler and Thomas[85] on the basis of mechanism of their production. These authors suggest dividing headaches into vascular headaches, including migraine, histamine, cephalalgia and tension headache; psychic headache; intracranial traction headache; extracranial headache due to irritation of afferent cranial or cervical nerves; combined intracranial and extracranial headache; and toxic or mixed headache.

Robertson et al.[86] have investigated the nature of pains in the head and face arising from diseased or experimentally stimulated teeth. Head pain associated with prolonged toothache and located at a distance from the painful tooth itself was found to be of two types. The first is that associated with sustained contraction of muscles of the head and neck, and the second that which is on the basis of referred pain in the distribution of the trigeminal nerve.

Ingraham and Cobb[87] have reported on their clinical experience with diodrast in cerebral arteriography, and state that this substance is safer than thorotrast and is as satisfactory in this procedure.

Falconer, McGeorge and Begg[88] have published a description of their extensive and careful study on the problem of ruptured intervertebral disk in the lumbar region of the spine. The results of routine myelography, done on patients suffering from low back pain, or sciatica, and admitted to the hospital because of severity or intractability of their symptoms, indicate that almost all such patients have intraspinal lumbar disk protrusion. A protruded disk may cause only low back pain, presumably through implication of the sinu-vertebral nerve. However, sciatica itself is produced only when the disk prolapse is so situated that it impinges upon a nerve root in its extrathecal course at the level of either of the lower lumbar vertebral disks. Secondary changes, probably on the basis of intraneural edema, appear within the affected nerve root, contributing to production of symptoms by pulling the nerve root tightly against the prolapsed disk and thus causing an angulating strain. In this manner pain fibers may be excited, and a block in neural conduction may be produced, thus accounting for certain of the sensory, motor and reflex disturbances seen in this condition. Resolution of these intraneural changes may result in spontaneous remission of clinical symptoms. It is interesting to note that in Falconer's series spontaneous remission of symptoms occurred in patients at a time when a prolapsed disk was still demonstrable by myelography.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35061

PRESENTATION OF CASE

A seventy-one-year-old unmarried woman entered the Tumor Clinic complaining of episodes of bloating and vomiting.

During the three months before admission to the Tumor Clinic she had experienced bouts of bloating, with nausea and vomiting, precipitated by food or drink. These episodes lasted only about one day and recurred on the average of once every three weeks. At the onset of the difficulty she had also noticed a feeling of pressure on the bladder, associated with urinary incontinence. About thirty years before admission she noticed moderate painless hematuria. About ten years later a suprapubic operation was done, and a "small growth" was removed. Her physician informed her that there would be a tendency for the tumor to recur, and she returned for many transurethral treatments for the purpose of cutting down the tumor. About sixteen years before admission she was told that the right ureter was closed. Operation was performed, and the ureter opened. It was kept dilated by cystoscopies and passages of ureteral sounds at weekly intervals and later less frequently. About three years before entry to this hospital, following an episode of hematuria, she entered another hospital, where two papillomatous tumors were removed from the bladder by suprapubic operation. At that time no function of the right kidney was demonstrable by intravenous pyelogram. About ten months later she re-entered the same hospital, complaining of a "lump" in the right side. A right nephrectomy and ureterectomy were done. The pathological report was "papillary carcinoma of pelvis and kidney."

Examination in the Tumor Clinic revealed an incisional hernia of the lower mid-abdomen and a firm, movable mass, about the size of a grapefruit, which could be ballotted between the abdominal and pelvic examining fingers on vaginal examination. On barium enema there was a large, extrinsic, tumor mass that displaced the rectum and lower sigmoid to the left. On intravenous pyelography the left kidney showed a slight dilatation of the calyxes and pelvis; the right kidney was not visualized. The mass in the pelvis had displaced the left ureter laterally, and there was questionable slight compression of the lower third of the left ureter. It also depressed the roof of the bladder. There was generalized osteoporosis of the bones of the lumbar spine and pelvis but no definite evidence of metastases. A chest film showed clear lungs. The heart was slightly prominent in the region of the left ventricle. A gastrointestinal series was negative except for a moderately large, easily reducible hiatus hernia. She was followed in the Tumor Clinic for about two months and then admitted to the hospital.

Physical examination revealed a thin woman. Abdominal examination disclosed a large, "cystic-feeling," movable, multilobular mass, apparently arising from the pelvis. On pelvic examination a mass was felt in the cul-de-sac, apparently connected with the abdominal mass.

The temperature was 99.8°F., the pulse 96, and the respirations 22. The blood pressure was 208 systolic, 90 diastolic.

Examination of the blood showed 12.2 gm. of hemoglobin and a white-cell count of 7500. The urine specific gravity was 1.004. The sediment contained 30 to 40 white cells per high-power field. The serum nonprotein nitrogen was 31 mg., and the total protein 6.3 gm. per 100 cc. The chloride was 106 milliequiv. per liter, and the prothrombin time was 22 seconds (normal, 16 seconds). A phenolsulfonephthalein test showed 40 per cent excretion of the dye in ninety minutes. An intravenous pyelogram, repeated about two and a half months after the one done in the Tumor Clinic, showed poor concentration of the dye. There was marked dilatation of the calyxes and pelvis. Only the upper third of the left ureter was seen, and this was dilated. The bladder was depressed but showed no definite defects. The mass in the pelvis had tripled in size since the time of the previous examination. A cystoscopy showed that only a third of the bladder mucosa could be visualized; no abnormalities were noted. The left ureteral orifice appeared normal. The mass in the pelvis so compressed the bladder that complete examination was not possible.

On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WYLAND F. LEADBETTER: We have several things to explain in this case: the episodes of vomiting, the mass in the pelvis, and the developing hydronephrosis and hydroureter on the left side. So far as the first part of the history is concerned, it seems quite obvious that for thirty years the patient suffered from recurrent tumors of the bladder. The type of tumor that might give rise

to recurrences without serious manifestations is a papillary tumor. It may have begun as a true papilloma of low-grade malignancy, or may have recurred as a papilloma or later as a papillary carcinoma. In any case, for fifteen of the thirty years she received treatment for recurrent bladder tumors.

Sixteen years before the last admission it was found that obstruction existed in the lower right ureter incident to either growth of the tumor or treatment therefor. I assume that as a result of the removal by fulguration or electroresection of one of the tumors the right ureteral orifice became scarred and ultimately closed. Operation was carried out to correct this obstruction, and the result must have been fairly satisfactory because up to three years before this admission cystoscopy was done at gradually increasing intervals for dilatation of the ureter. Hematuria recurred at this time, and the patient was found again to have a papillary tumor of the bladder. This one was removed by suprapubic operation. At that time no function was demonstrated in the right kidney. This brings up the point that many papillary tumors of the urinary tract may have their origin in the renal pelvis or ureter with secondary involvement of the bladder. Whether bladder tumors under these circumstances arise independently as a result of some carcinogen excreted in the urine or by implantation of tumor cells on the bladder mucosa from the renal pelvis or ureter, I do not know. In any case, we have found from experience that if we are dealing with a papillary tumor of the bladder we must at least obtain an intravenous urogram to determine whether there is evidence of tumor in the upper urinary tract. In a significant number of cases we find associated papillary tumor of the renal pelvis or ureter. In the case under discussion there was a papillary tumor of the right renal pelvis or ureter, because two years before the patient entered this hospital a nephroureterectomy was done. The record states that a "papillary carcinoma of the pelvis and kidney" was found. It would be interesting to know whether the ureter was involved because it might have a bearing on subsequent events. If transection of the ureter occurred through tumor, or if tumor cells from the ureter were spilled, it is possible that a recurrence of papillary carcinoma took place outside the bladder wall in the pelvic tissues. Up to this point in the case we can be quite certain of the state of affairs.

When the patient came to the Tumor Clinic it was found that she had a firm, movable mass about the size of a grapefruit in the pelvis. This could be palpated easily on combined abdominal and vaginal examination. It implies that the tumor was not deeply infiltrating or fixed to the pelvic wall. There is no statement referable to the pelvic organs, which is unfortunate because there is no way of knowing whether there was disease of the uterus or adnexa. It therefore seems impossible to make a definite diagnosis.

DR. TRACY B. MALLORY: Can you give us any further information on that point, Dr. Sturgis?

DR. SOMERS H. STURGIS: No. I just saw her on entry to the hospital two months later.

DR. LEADBETTER: I think one can assume that this mass did not suggest disease of the cervix. I do not think we can carry it any farther than that. A barium enema showed nothing in the lower bowel. Intravenous pyelograms showed dilatation of the left renal pelvis and ureter. There could have been intrinsic disease of the left lower ureter or pressure on the ureter by the mass in the pelvis. A mass of this size would cause pressure on and distortion of the bladder.

There was generalized osteoporosis of the bones of the lumbar spine and pelvis, but no definite evidence of metastasis. I do not like the statement "no definite evidence." It implies to one reading the record that the radiologist was suspicious of metastatic disease in the bone but unwilling to commit himself. The chest films were normal. A gastrointestinal series was negative except for hiatus hernia, which probably has no bearing on our problem. In the two months that intervened between examination in the Tumor Clinic and entry to the hospital, the pelvic mass changed markedly in size, consistence and configuration. What happened during the two-month interval is difficult to say. If we are dealing with cancer, necrosis or hemorrhage or both may have occurred, or the tumor itself may have simply grown tremendously.

The presence of white cells in the urine is not significant since it is improbable that cystoscopic treatment could have been repeatedly carried out for thirty years without some infection being present. One is obliged to make the diagnosis of cystitis, and possibly, of low-grade pyelonephritis of the left kidney. The nonprotein-nitrogen was normal but the phenolsulfonephthalein test showed diminished excretion in ninety minutes. An intravenous urogram showed poor function, with dilatation of the pelvis and ureter, which had increased a great deal in two months. Cystoscopy was reported to allow incomplete visualization of the bladder interior, but no abnormalities were noted.

The question of tumor involving the bladder wall comes up, and with the information at hand it is difficult to be sure that such a tumor was not present. It is a possibility. In view of the dilatation of the left upper urinary tract, it would be desirable to know whether intrinsic disease of the left lower ureter existed. It could have been determined by ureterogram. I would not have wanted to operate without knowing something more about this.

From the standpoint of diagnosis my explanation seems too easy to be true and there is probably some catch, but I think the most likely possibility is that

recurrent papillary carcinoma developed outside the bladder wall in the tissues behind the bladder, either from spillage of cells at the time of ureterectomy or from tumor cells in the intramural ureter, which may not have been removed. If we knew the condition of the pelvic organs prior to the development of the mass, diagnosis would be much easier.

For the sake of completeness we have to consider other possibilities. Since papillary tumors of the bladder had been repeatedly treated, it is possible that extension through the bladder wall occurred, even though the bladder lumen showed no evidence of tumor. Involvement of lymphatics in the pelvis is possible. The mass may have originated in the iliac or hypogastric glands, but the description of the mass as ballotable leads one to believe that it did not arise in the pelvic wall itself. It could have been, I suppose, an ovarian neoplasm or a mass in the fundus of the uterus. We have to consider the sigmoid as the point of origin in spite of the normal barium enema — cancer of the bowel or an abscess arising in an infected diverticulum of the sigmoid. These possibilities seem very unlikely. A diverticulum of the bladder, with a very tiny communication with the bladder, and a perivesical abscess originating in infection at the time of operation two years before, are remote possibilities. Lymphosarcoma, retrovesical sarcoma or sarcoma arising in the bladder wall are mentioned but excluded because of the lack of fixation of the mass. A ruptured aneurysm of a pelvic vessel is dismissed as extremely unlikely.

Dr. F. Dennette Adams: Would you expect carcinoma — that is, recurrent carcinoma — to be as movable as this mass was?

Dr. Leadbetter: Papillary carcinoma may not be a markedly infiltrating tumor. It may form a mass without extreme fixation.

Dr. Langdon Parsons: How often do tumors of the genitourinary tract metastasize to the ovary?

Dr. Leadbetter: I have never seen it, but in going over a series of 100 cases of bladder cancer autopsied at the Johns Hopkins Hospital, I believe I found 2 or 3 cases metastasizing to the ovary.

Dr. Joe V. Meigs: A Krukenberg tumor of the ovary may come from a tumor of the stomach, uterus, bile ducts or rectum, but I never remember it from the kidney or ureter. I think it could happen.

Dr. Leadbetter: I should have mentioned the possibility of carcinoma of the gastrointestinal tract with peritoneal implant in the cul-de-sac.

Dr. Meigs: There was no blood in the urine to any extent, which might be odd if the tumor extended directly from the bladder to the pelvic wall.

Dr. Leadbetter: Yes.

May we see the x-ray films?

Dr. Stanley M. Wyman: The lung fields are clear. The heart is definitely enlarged, but without characteristic configuration. The barium enema outlines an ill defined, soft-tissue mass occupying most of the pelvis centrally, displacing the sigmoid and rectum toward the left, but it does not appear to involve the colon intrinsically. The first pyelogram shows prompt excretion of dye by the left kidney, with blunting of the minor calyxes, slight widening of the major calyxes and definite displacement of the left midureter. The left ureter can be seen on a later film, displaced far to the left. In the left pelvis the bladder shadow shows some compression laterally. Again the outlines of the mass in the pelvis are indistinct. There is no unusual calcification or rarefaction. Examination done about two months later shows a definite increase in the size of the pelvic mass, which now rises out of the pelvis. The left kidney is seen to be tremendously increased in its degree of hydronephrosis. The left ureter can be followed only for a short distance. Examination of the stomach shows a hiatus hernia as described. The available films fail to reveal any definite intrinsic disease of the stomach itself. There is some suggestion of poor filling of the medial aspect of the duodenal loop, but I can make no further statement about that.

Dr. Leadbetter: On viewing the x-ray films, I must say that the mass is larger and growing more rapidly than I had supposed from reading the record. It suggests that the lesion was a cystic tumor arising from the pelvic structures, probably the ovary. I have to retract my impression of recurrent carcinoma originating in the urinary tract.

Clinical Diagnosis

Malignant ovarian cyst.

Dr. Leadbetter's Diagnoses

Cystic ovarian tumor.
Hydronephrosis and hydroureter, left.
Chronic cystitis.

Anatomical Diagnosis

Metastasis of papillary carcinoma of bladder to ovary.

Pathological Discussion

Dr. Sturgis: When this woman came into the hospital she had this tremendous tumor, filling the whole pelvis. It was somewhat fixed on the right side. We thought she had an ovarian cyst, probably malignant. This is why we operated, but I cannot explain the tripling in size during the short period of observation. We found that she had an ovarian cystic tumor definitely arising from the right ovary. It was very large, and in bringing it up we ruptured it. It was filled with dark, chocolate material, and was a papillary type of malignant growth in the ovary. The patient was seventy-one years old and had only one kidney, and because of the fear of spillage we did not do

more than remove the right ovary and closed her up. The uterus was tiny and atrophic. We believed that we were not justified in prolonging the operation for the sake of more accurate diagnosis.

DR. MALLORY: The mass that reached the laboratory looked like an ordinary papillary serous cystadenoma of the ovary; on gross examination there was no question of what it was. On microscopical examination we found that the entire mass was lined with characteristic transitional epithelium; it looked exactly like a bladder papilloma, and I think, without doubt, it represented metastasis to the ovary, from a primary bladder or ureteral tumor. The tumor cells were those of a low-grade type of papillary carcinoma.

DR. LEADBETTER: Why did the mass increase in size so rapidly? Because of hemorrhage?

DR. MALLORY: The cyst contained a large amount of fluid, and there had been hemorrhage into it.

DR. STURGIS: That is what we thought.

DR. MEIGS: Could it not have started in a dermoid type of teratoma that contained a transitional type of epithelium rather than as a metastatic lesion?

DR. MALLORY: I do not believe so. If I gave you a section of the wall of the ovary, I think you would, without hesitation, say that it was a characteristic bladder tumor. Whether or not the ovary was previously cystic, I do not know. It is possible that the metastasis occurred into an already cystic ovary. I cannot answer that.

DR. MEIGS: Frequently tissue in the ovarian dermoid or teratoma resembles tissue from other parts of the body that can grow. We often see tumors that resemble the thyroid gland. We see intestinal or endocervical mucosa from which a pseudomucinous cystadenoma arises, so why cannot that kind of epithelium be found in a dermoid?

DR. MALLORY: In theory any type of tissue may develop in a teratoma; in practice I have never seen an ovarian cyst with this type of lining. The only type of ovarian tumor containing transitional epithelium is a Brenner tumor; that has a different appearance.

DR. MEIGS: And a Brenner tumor can also be associated with dermoid, can it not?

DR. MALLORY: I have never heard of a Brenner tumor becoming malignant, however.

DR. MEIGS: I have not either.

DR. PARSONS: Was there any bone element?

DR. MALLORY: We found none.

CASE 35062

PRESENTATION OF CASE

First admission. A fifty-three-year-old housewife was admitted to the hospital because of "asthma and exhaustion."

Before the age of forty the patient experienced occasional episodes of mild wheezing and dyspnea with exertion. These were not particularly troublesome and were attributed to obesity. When she was forty she had rather severe "asthmatic attacks," which disappeared spontaneously after a few days. Since that time she had almost continuous year-around attacks, which could not be related to place or season. Three years before admission she was studied in another hospital, where she was said to have been allergic to goats, feathers and chocolate. She stated that the attacks became worse upon contact with these substances. Episodes of nervousness and tension also increased the symptoms, and because an active social life tended to aggravate her condition she had recently lived a rather secluded life. The last severe attack began about two months prior to admission at which time she was admitted to another hospital, where she gained some relief.

The patient's general health had "always been poor." An attack of rheumatic fever when she was seven was followed by sore throats three or four times yearly until the age of thirty-five, when a tonsillectomy was done. She had suffered frequent attacks of sinusitis, for which she was operated upon twice. During one period she took desiccated thyroid for obesity and developed marked tachycardia, nervousness and tremor. She had suffered bouts of diarrhea, lasting three or four days, coming on every three or four weeks, for the past four years. There was no history of chest pain or ankle edema.

Physical examination revealed a well developed and well nourished woman with slight asthmatic breathing. The neck veins were not distended, and the chest was symmetrical with increased anteroposterior diameters. There was moderate emphysema, with decreased fremitus and hyperresonance. There was questionable wheezing on the right side anteriorly. The point of maximal impulse was 1 cm. beyond the midclavicular line, and a Grade I systolic murmur could be heard at the apex. The rhythm was normal, and the pulmonic second sound was not loud. The liver edge was felt 1 cm. below the costal margin.

The temperature was 99.5°F., the pulse 115, and the respirations 24. The blood pressure was 140 systolic, 60 diastolic.

The urine was normal. The blood hemoglobin was 16 gm.; the white-cell count was 8000, with 76 per cent neutrophils. The blood sugar was 116 mg., the nonprotein nitrogen 11 mg., and the total protein 4.4 gm. per 100 cc. A roentgenogram of the chest disclosed fairly large lung fields, with some increased density posteriorly in the costophrenic angle. The diaphragm was low in position and showed some limitation of motion. The heart was in the upper limits of normal in size. Many scratch tests, including those for feathers and goats, were negative.

The patient continued to have dyspnea and spells of coughing. There was cyanosis of the lips and nail beds. On the eleventh hospital day the blood hemoglobin was 14.4 gm., and the total protein 5.02 gm. per 100 cc., with an albumin-globulin ratio of 1.6. The blood sodium was 138.1 and the chloride 95 milliequiv. per liter; the nonprotein nitrogen was 19 mg. per 100 cc. On the seventeenth hospital day a "sore throat" developed, following which orthopnea and wheezing became worse. When sitting up in bed she was cyanotic, but upon lying flat much of this disappeared. The neck veins were distended, and there were rales in the chest. She was given several injections of mercuhydrin, after which she showed slow but steady improvement. She was discharged on the thirtieth hospital day.

Final admission (approximately three weeks later). In the interval the patient experienced little dyspnea or wheezing, although she remained in bed most of the time. One week before entry, however, she noticed swelling of the ankles and abdomen, although orthopnea and breathing were no worse. She was given several injections of mercurials to no avail.

On physical examination the patient breathed somewhat heavily but without audible wheeze. There was no cyanosis; the neck veins were distended. There were rales in both bases, and the heart findings were essentially the same as on the previous admission. The liver edge was palpated four fingerbreadths below the costal margin, with tenderness in the right upper quadrant. There was a +++ pitting edema of the ankles and ++ edema over the sacrum.

The temperature was 98°F., the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 60 diastolic.

The urine gave a + test for albumin. The blood hemoglobin was 13 gm.; the white-cell count was 9400, with 73 per cent neutrophils. The blood sugar was 148 mg., and the cholesterol 231 mg. per 100 cc.

The patient's condition did not improve. She refused to eat a salt-free diet. A roentgenogram showed a suggestion of fluid in the right costophrenic sinus, and the heart shadow appeared slightly larger than before, the enlargement appearing to be chiefly in the region of the left ventricle. An electrocardiogram showed sinus tachycardia at a rate of 100, with a PR interval equal to 0.15 second. There was moderate right-axis deviation and a tendency toward low voltage in all limb leads. There was a low and upright T wave in Lead 1, depressed ST segments with diphasic T wave in Leads 2 and 3. The T waves were diphasic in Lead VR, low and upright in Lead VL, diphasic in VF and upright in V_3, V_4 and V . The ST segments were depressed in Lead VF.

On the fourth hospital day the blood sodium was 135.2 and the chloride 83 milliequiv. per liter. Four days later the blood carbon dioxide was 44.1 milliequiv. per liter. On the eleventh hospital day the red-cell count was 5,810,000, the hemoglobin 13.6 gm. and the pH 7.35. The patient became progressively more cyanotic but with little orthopnea. There were rales in the right base but normal breath sounds. There was ++++ edema of the lower extremities, and ++ edema over the abdominal wall. The abdomen was distended, and shifting dullness was present. On the sixteenth hospital day the serum protein was 6 gm. per 100 cc., and the potassium 5.4, the sodium 138.8 and the chloride 83 milliequiv. per liter. She was given mercurial diuretics intermittently, with irregular response. Oxygen relieved much of the cyanosis. During the following several weeks periods of improvement alternated with periods of relapse, although the course was progressively downhill. On the forty-fifth hospital day the patient began fibrillating; the temperature, pulse and respirations rose, and two days later she died.

Differential Diagnosis

Dr. J. Evarts Greene: This patient is said to have had occasional episodes of mild asthma or at least mild wheezing and dyspnea on exertion before the age of forty. There is no record of such symptoms without exertion; they were attributed to obesity, but it is possible that they were due to early emphysema or low-grade chronic bronchitis. When she was forty she had what was described as a severe asthmatic attack, and thereafter she had asthma the year round without relation to place or season. Forty years of age is the time, as Dr. Rackemann has frequently emphasized, when intrinsic asthma begins to be much more frequently noted than extrinsic. I think the fact that she had her symptoms all year round, without relation to season or place, but increased by nervous tension, is in favor of a diagnosis of intrinsic asthma. She may have had minor allergies, but they certainly did not play an important part in her final illness. Her general health was always poor. She had early rheumatic fever, many sore throats and attacks of sinusitis. I cannot relate these conditions to the complaints that led to death. She is also said to have suffered from repeated diarrhea, apparently quite frequently, every three or four weeks.

I would like to ask if any stool specimens were examined for amebic cysts.

Dr. Francis M. Rackemann: No.

Dr. Greene: If the patient had amebic colitis, it could hardly have had any bearing on what happened later. On physical examination she had signs of emphysema and mild asthma. There was questionable wheezing on the right side. The liver edge was felt 1 cm. below the costal margin. The blood

pressure was 140 systolic, 60 diastolic — certainly not a low pressure.

The laboratory findings, except for moderately low total protein, do not seem remarkable. X-ray examination is said to have shown fairly large lung fields, with increased density posteriorly in the costophrenic angle. May we see the films?

DR. STANLEY M. WYMAN: The films taken on the first examination show the density described in the posterior costophrenic sinuses, which I believe represents a small quantity of fluid in both pleural spaces. Increase in the anteroposterior chest diameter is quite well shown. The lung fields themselves seem rather large and somewhat bright for a patient of this size. The heart shadow is at the upper limits of normal, without definite characteristic configuration, however. I think we should add that the hilar vascular shadows are increased in prominence, and the proximal portions of the pulmonary artery in both lung fields are somewhat engorged. I cannot see any definite localized pulmonary disease, however.

Examination two months later shows a definite but small quantity of fluid in the right costophrenic sinus and possibly on the left. The heart shadow may be a little larger. This is not a very conclusive finding. The third examination has not, so far as I can see, changed materially. I think the statement that the left ventricle appeared to be large is wrong; I think this simply emphasizes to us once again that we cannot differentiate well left ventricular from right ventricular enlargement in the presence of engorged pulmonary vascular shadows. Right ventricular enlargement is more consistent with this picture.

DR. GREENE: There is no evidence of pulmonary fibrosis?

DR. WYMAN: We looked carefully for diffuse pulmonary fibrosis because we thought that this patient had cor pulmonale but were unable to be certain of diffuse fibrosis. I know that it can be completely missed on x-ray examination, however.

DR. GREENE: Did you find anything suggesting calcification of the pericardium?

DR. WYMAN: No, neither fluoroscopically nor on the films.

DR. GREENE: The skin tests done here were apparently negative. The patient continued in the first hospitalization to have dyspnea and coughing, with cyanosis.

I do not think the blood chemical findings, except for the total protein, were significantly altered. On the seventeenth day the patient was said to have developed a "sore throat." I am not sure whether that means that no one could see an inflammatory process. At least orthopnea and wheezing became worse.

"While sitting in bed she was cyanotic, but upon lying flat much of this disappeared." I do not know what that statement signifies. I have seen an occasional patient with emphysema who stated that he was a good deal more comfortable lying down than sitting up. Usually, such patients merely state that they are not more uncomfortable lying down than sitting up. On the other hand, the patient is said to have had orthopnea at this point, but why the cyanosis disappeared on lying down, I cannot say. During the interval between hospitalizations, swelling of the ankles progressively increased. On the second hospital admission the liver was markedly enlarged, and again the neck veins were distended but there was no cyanosis.

DR. RACKEMANN: I do not think that is correct. As I recall, there was cyanosis all the time.

DR. GREENE: The blood sugar was 148 mg. per 100 cc.; that is an isolated finding, and I am tempted to disregard it. The heart was more enlarged, and electrocardiographic findings seem consistent with right-sided failure. I would be interested in hearing the cardiologists say a word about the unipolar leads.

DR. CONGER WILLIAMS: They do not add a thing; I have been over them, and they do not help at all.

DR. GREENE: The carbon dioxide of 44 milliequiv. per liter — a somewhat elevated figure — is consistent with emphysema. Patients with emphysema are supposed to have difficulty in eliminating carbon dioxide. During the second admission the red-cell count rose, consistent with passive congestion and emphysema. There was no definite acidosis, and the potassium was said to have been elevated. That is sometimes found in allergic episodes. I do not believe an acute allergic episode was involved at this stage of the game. It seems that the patient was going downhill slowly, with right-sided heart failure, and that she died for that reason.

In discussing the possible diagnoses we can dismiss the possibility of such conditions as nephrosis, amyloidosis and cirrhosis of the liver, which might cause swelling of the legs and abdomen, because they would not account for cyanosis or dyspnea. I think that asthma and pulmonary emphysema, followed by cor pulmonale, with right-sided heart failure and chronic passive congestion, would give a satisfactory explanation of this patient's illness. There is a possibility also, although it seems unlikely, that she had chronic constrictive pericarditis, which certainly could have caused the cyanosis and the swelling of the extremities and abdomen. However, as evidence against this, the patient apparently improved on mercurial diuretics, at least temporarily; she did not show any sign by x-ray study of pericardial thickening, and there was no history of antecedent illness to account for it. Ayerza's disease must be considered as a possibility, but I do not think we have enough definite data to make that diagnosis. Periarteritis nodosa is occasionally associated with asthma, but I cannot see that we have any definite reason to make a diagnosis of that condition. So I come back to my

first diagnosis of asthma, emphysema, cor pulmonale and right-sided heart failure.

DR. RACKEMANN: We had quite a time with this patient. I do not think the history gives quite a true picture of what was going on. The attack that she had at the outside hospital before she came in here was quite obviously asthma. She came in here three months before she died. The low serum protein on the first admission was quite striking. The connection of this finding with her other symptoms was hard to determine, and what caused the cyanosis was hard to say. There was some asthma, — a little shortness of breath, — but it was not striking at that time. There was no evidence that I could see of any strain on the right side of the heart. However, the consultants, Drs. Bland and Williams, showed that I was wrong — that the cyanosis could be interpreted on the basis of right-sided heart failure. She went home in fair shape. Three weeks later she came in again, and the picture was entirely different. The cyanosis was still present, but she had a full-blown picture of right-sided heart failure, with severe pitting edema of the extremities, fluid in the abdomen and soft, pitting edema of the abdominal wall. That bothered us a good deal. Why did she have edema? Why did she not improve with digitalis and mercurial and other diuretics? It was all very puzzling. The story of asthma did not seem severe enough to produce the strain on the right side of the heart, considering that so many people have the same story with no such terminal findings. Then, as we went on, it became clear that she could not get rid of the excessive carbon dioxide. The heart seemed normal; the pulse was regular, the rate being elevated to 100 or sometimes 110. Days and weeks went by, and very little change occurred in the *status quo*. Except for the continuous edema, the heart seemed to function reasonably well. So then we began to think about other reasons for obstruction of the blood flow from the right side of the heart, and that led us to lean toward the diagnosis of Ayerza's disease.

DR. WILLIAMS: I have little to add. I was interested in one thing — namely, that in several reported series of patients with cor pulmonale secondary to pulmonary asthma the patients had been entirely or predominantly of the male sex. I think it is a little unusual for someone to develop pulmonary fibrosis, or whatever one chooses to call this syndrome, in such an apparently short time on the basis of asthma alone. I do not see any other explanation for it, however.

DR. DONALD S. KING: In the past we have not had to have changes in blood vessels; emphysema occurred alone with this much right-sided failure.

CLINICAL DIAGNOSES

Cor pulmonale.
Pulmonary endarteritis.
Ayerza's disease.

DR. GREENE'S DIAGNOSES

Bronchial asthma.
Pulmonary emphysema.
Chronic cor pulmonale.
Right-sided heart failure.

ANATOMICAL DIAGNOSES

Pulmonary emphysema.
Pulmonary arteriosclerosis.
Cor pulmonale.
Terminal thrombosis of pulmonary arterioles.
Acute central necrosis of liver.
Adenocarcinoma of thyroid gland.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Autopsy showed voluminous emphysematous lungs, with large blebs in them. The pulmonary vessels demonstrated numerous atheromatous plaques, and the small pulmonary arteries and arterioles contained thrombi very diffusely and extensively throughout the lung. These thrombi were rather friable and slightly adherent to the vessel wall. At the time of autopsy we thought they might show early organization. Microscopical sections failed to confirm that entirely. The thrombi must have been of quite recent origin — I should think certainly less than a week's duration, perhaps three to five days — so they can be regarded only as a terminal event. The heart weighed 420 gm., and the right ventricle was 9 mm. in thickness, a marked grade of cor pulmonale. The liver showed an extreme degree of passive congestion, with acute terminal central necrosis, which, I think, was perhaps of the same duration as the acute process in the pulmonary arteries. There was an incidental finding — a markedly nodular thyroid gland, and one of the nodules showed early carcinomatosis. That had nothing to do with the symptomatology, however. From the anatomic point of view, the only diagnoses are emphysema, pulmonary arteriosclerosis, cor pulmonale and a terminal episode of acute thrombosis of the small pulmonary arteries. The picture was not what one ordinarily calls Ayerza's disease — long-standing apparently primary disease in the pulmonary arteries.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

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MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

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COMMUNICATIONS, *including those concerning classified advertising but not those regarding other advertising*, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

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MEDICAL MONOPOLISTS

WHILE physicians argue among themselves over the most effective method by which their relations with the public can be improved, the lay public is being enlightened in a number of ways. One of the most recent is an article by J. D. Ratcliff in the *Woman's Home Companion* for October, 1948, that has been announced in full-page advertisements in various newspapers. With a foreword by Dr. Allen O. Whipple, former president of the American Board of Surgery, it exposes the "medical monopolists" who keep brilliant young doctors out of hospital staffs for fear of competition. For human interest it tells the story of "brilliant young Dr. Jim Smith — straight A's" — and how he was "barred from practice in hundreds of communities by men with a fraction of his skill." The punch line is that so long as this deplorable situation goes unremedied, the community "will continue to get 1920 medicine for 1948 ills."

No exception can be taken to the article itself. Were it published to be read only by the medical profession it would amount simply to a necessary display of dirty linen in urgent need of washing. Directed to the lay public, however, and accompanied by an exhortation to "civic-minded individuals and organizations" to send for free reprints and then to "bring public opinion to bear," it becomes a subtle piece of propaganda in favor of state medicine. Its most effective feature is its omission of any reference to state medicine.

For who can doubt the direction in which such civic-minded public opinion would be directed? And on whom would the pressure be exerted? It would be "brought to bear" on the congressmen who are already considering bills for governmental control of the practice of medicine.

But is that the way to remedy this admittedly deplorable situation? By what laws have morals ever been successfully dictated? Deplorable economic and political situations exist about which the individual physician can do little or nothing — the high cost of medical care, the high price of medical education and the shortage of hospital beds, to mention only a few — but this "medical monopolist" situation is one piece of dirty linen that the medical profession should be able to wash for itself because it is essentially a moral situation. That the leaders in the profession are aware of its existence and are eager to put a stop to it is evident in the presidential address delivered last fall before the New England Surgical Society and published elsewhere in this issue of the *Journal*. Wherever it may exist it is a cynical betrayal of the public confidence, a brazen violation of the Hippocratic oath and a selfish denial of the basic purpose of the whole medical profession. A better punch line would have been: wash day is here — if you doctors don't want to be taken to the cleaners by force, start washing!

THE THERAPEUTIC ROLE OF THE KEMPNER DIET

DIETARY restriction of one sort or another has been utilized in the treatment of hypertensive disease for many years. In 1945 Kempner[1] presented the details of his commendably aggressive approach to the dietary treatment of this group of diseases and thereby stirred up a great deal of comment, both medical and lay. Kempner's own therapeutic results are little short of miraculous and have justifiably impressed numerous competent and critical observers who have visited the North Carolina clinic. Investigators other than Kempner have obtained favorable, but not miraculous, results in most cases, and the chief difficulty seems to center around the extreme monotony of the diet. Most physicians lack the extraordinarily persuasive powers required to keep a patient eating rice and certain types of fruit for weeks, months or even indefinitely. The usual result is that the patient fails to eat all the food presented to him and, not infrequently, finally rejects the diet altogether.

Kempner's claim that patients following his regimen remain in nitrogen balance is adequately refuted by recent balance studies.[2] Regarding maintenance of weight on the Kempner diet there is further disagreement between Kempner and other workers. Kempner finds that patients receiving the diet lose weight initially but after some weeks the weight becomes stable and all is well — in fact, so well that the diet can often be modified slightly. He attributes the initial loss of weight to loss of fluid. It has proved very difficult for other investigators to confirm or deny these claims, mainly because so many patients cannot conform to the rigid requirements of the Kempner regimen over long periods. It seems clear, however, that patients receiving the Kempner regimen in clinics other than Kempner's own lose not only fluid but also body tissue. The diet, as it usually works out in practice, is a specialized sort of starvation ration, and the contention that it is adequate in calories and protein needs modification.

It is entirely possible that the tendency for patients on the Kempner regimen to eat less than the stipulated amounts of rice and fruit can be used to advantage in certain types of cardiac disease with failure. Salt restriction in such patients is unquestionably highly important. Reduction in weight over and above that due to fluid accumulation is crucial in many obese patients with cardiac failure. Heretofore the patient has been offered a low-calorie diet, which often supplies 800 calories or less, to achieve loss of body tissue. He has been implored and cajoled not to eat more than the allowed amount, in spite of which he often reaches a point where he secretly takes extra food and the physician cannot understand why the patient's weight remains too high. The psychologic, as well as the physiologic, advantages of the Kempner regimen in this situation seem not to have been appreciated. Using the rice-fruit diet, the physician, instead of pleading with his patient to eat less, actually has to urge the patient to eat all the food given him. The very low salt intake, a difficult feature to control on any sort of hospital diet other than that devised by Kempner, helps to rid the patient of excessive fluid, and concurrently, the usual inability to maintain the caloric intake allowed by the Kempner regimen causes a reduction in body fat and protein. Practically speaking, there probably is no more effective diet for obese decompensated cardiac patients.

Although the Kempner regimen is certainly not the final answer in the treatment of hypertensive disease, it is an important development in the search for a practical and uniformly successful method of treating the disorder. Furthermore, it may well find a permanent place in the treatment of some types of congestive cardiac failure and even in uncomplicated obesity.

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1. Kempner, W. Compensation of renal metabolic dysfunction: treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M. J.* 6:61-87 and 117-161, 1945.
2. Schwartz, W. B., and Merlis, J. K. Nitrogen balance studies on Kempner rice diet. *J. Clin. Investigation* 27:406-411, 1948.

THE ZISKIND RESEARCH LABORATORIES

DURING the past quarter century the evolution of medical knowledge has brought into action a centripetal force that crowds together groups of interests and activities formerly carried on as separate endeavors. Medical education and medical care were the first to merge, and their common interests have produced in many parts of the nation a type of institution aptly described as the univer-

sity hospital. In New England the same joining of interests has taken place, but we do not have university hospitals as such, preferring to enjoy the obvious advantages without merging the identity of either institution into the other. Our arrangement calls for a little more understanding on the part of all concerned, but this is only a greater stimulus to cooperation and recognition of the common cause. As these centripetal forces continue, what are becoming known as medical centers are formed. In a modern medical center there appear to be not two, but three major interests: medical education and medical care find themselves in the presence of a third party, medical research. How to make elbow room for this new and essential interest has already become a problem in many centers.

At the New England Medical Center the solution of the problem was dedicated on November 11, 1948, at the formal opening of the Ziskind Research Laboratories. In a seven-story building 24,000 square feet of floor space are already equipped and in use, another 36,000 feet are ready to be equipped in the near future, and a total capacity of 96,000 square feet is available in the potential capacity of the building as a whole. The two floors now in use are connected by a bridge with the Joseph H. Pratt Diagnostic Hospital, which in turn is connected with the other units of the Center.

Mr. Jacob Ziskind's generosity has thus solved the problem of adequate physical facilities for research at this center for many years to come. But, as is so often the case and as was pointed out at the dedicatory exercises, the solution of one problem creates another; how may the research activities best fit themselves into the programs of medical care and medical education already underway? In discussing the necessity for careful integration of these elements it was stated that an effort would be made to have the staff fall into three broad categories: bedside clinicians, basic research scientists and a group who might be termed "clinical scientists." The clinical scientist would attempt to be conversant with the problems both of the bedside and of the laboratory. The center would then have to rely for its fullest development on the combined efforts of these three groups. With such a staff it is hoped that a smooth transition from the laboratory to the bedside can develop. So the evolutionary processes go on.

POSTGRADUATE LECTURE COURSE

With the fourth annual postgraduate lecture course in general medicine impending, it is rapidly becoming a midwinter tradition to give it the usual journalistic introduction. There seems to be no reason why this course should not take equal rank with the better known of the various winter carnivals; perhaps even with New Orleans's famous Mardi Gras — less spectacular but still more instructive.

Arranged by the efficient and far-sighted Committee on Postgraduate Education of the Massachusetts Medical Society, the course will again be given in Sanders Theater, Harvard University, Cambridge. It will run, as usual, on Mondays from 6:00 to 9:00 and on Wednesdays from 4:00 to 6:00 p.m., beginning this year on Monday, March 7, and closing on Wednesday, April 27. An outline of the program is printed elsewhere in this issue of the *Journal*, and the full program will be published shortly.

A feature of the 1949 program will be the discussions planned for March 7, built around the subject of "A Positive Program for the Health of the Public." This program, on the "hottest" subject in medicine today, will be under the joint chairmanship of Dr. James S. Simmons, dean and professor of public health at the Harvard School of Public Health, and Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society.

Participating will be Dr. Hugh R. Leavell on "Local Health Departments," Dr. Samuel B. Kirkwood on "Maternal and Child Health," Dr. Stuart S. Stevenson on "School Health," and Dr. Albert O. Seeler on "Industrial Health." All the speakers are from the Harvard School of Public Health.

The course is free to all physicians residing in New England, regardless of membership in any medical society. Those who wish to register immediately for the course should do so by writing to the Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston.

BOSTON MEDICAL LIBRARY

PERSONNEL

Mr. Charles C. Colby, III, joined the Library staff the first of the year as reference librarian, succeeding Miss Catherine Binderup. Mr. Colby has an excellent background for the position, with the degree of A.B. from Harvard University in the field of biology (1943) and S.B. from Simmons College Library School (1947). He has had one year of a premedical course at Yale University and half a year in the basic medical sciences at Harvard Medical School. From the time of his graduation from Simmons College in June, 1947, until the end of 1948 he was employed as a cataloger at the Army Medical Library in Washington.

EXHIBITS

Concurrently with the meeting of the American Numismatic Society held in Boston in 1948, an exhibit of medals and coins of medical significance dating from the Roman period to modern times was placed in the rotunda at the Library. Through the courtesy of Dr. Elliott P. Joslin, the two diabetes medals awarded to survivors of the disease over long periods by the George F. Baker Clinic were also displayed. Dr. Paul Mueller, who recently received the Nobel prize for his discovery of DDT, was the subject of another exhibit, which included his portrait, his original article on his investigations, a sample of the insecticide and other material.

IMPORTANT ACCESSIONS

The Library is interested in the work of René Descartes, especially in the fields of knowledge related to medicine. The Library recently had the opportunity of obtaining a good, small collection of his publications, including the definitive edition of his collected works, published under the auspices of the minister of public instruction of the French Republic in twelve volumes (Paris, 1897–1910). This edition was reserved primarily for French libraries and institutions and is consequently a scarce set outside France. Unfortunately, it is printed on very poor paper that will not survive the ravages of use and time. There are also the *Opera philosophica* (Frankfurt, 1792-1797) in three volumes, and the *Oeuvres*, published by Victor Cousin (Paris, 1824-1826) in eleven volumes and an atlas. The Library already owned three early editions of *De homine*.

The reference division has been enriched by the acquisition of the Edwards reprint of the British Museum Catalogue, an essential tool for medical bibliographical research.

NEW PERIODICALS

The following sets have been added to the periodical division:

American Journal of Orthopsychiatry (Menasha). Vol. 8 to date. The Library needs Vol. 1 to 7 to complete this important set.
Folia cardiologica (Milan).
Helvetica medica acta (Basel).
Revista Espanola de cirurgia (Madrid).
Revue d'hématologie (Paris).
Revista do Instituto Adolfo Lutz (São Paulo).

The Library has subscribed to the complete series of the *Excerpta medica*.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

END OF DISTRIBUTION OF DRIED PLASMA BY RED CROSS

Dr. Harry Kleinschmidt, director of health services of the North Atlantic Area of the American National Red Cross, has notified Dr. Vlado A. Getting, commissioner of health for Massachusetts, that no further shipments of surplus dried plasma will be made after December 31, 1948. The supply of dried plasma turned over to the Red Cross after VJ Day is now reported to be so low that nationwide distribution cannot be continued. Dr. Kleinschmidt expressed the hope that sufficient whole blood would be collected by the National Red Cross Blood Program to provide whole blood, plasma and fractions for the entire country.

Distribution of this plasma in Massachusetts during the past two years has been effected through the Division of Biologic Laboratories, 375 South Street, Jamaica Plain, Boston. At the present rate of distribution, the residual supply on hand at the Jamaica Plain depot will last until April 1, 1949. Hospitals are urged to conserve the plasma as much as possible until the Red Cross Blood Program is able to replace it with new material.

SEROLOGIC TESTS ON CONVALESCENTS FROM INFLUENZA

The Department is co-operating with the National Influenza Information Center by attempting to determine the type of influenza virus present whenever the disease becomes prevalent. The Department is asking the co-operation of physicians in all parts of the Commonwealth in sending in acute and convalescent blood specimens on a small representative sample of the most suspicious cases occurring in an area where the disease appears to be prevalent.

Attention is called to the fact that this is *not a diagnostic test*. Information about the type will not become available until the patient is in the *convalescent stage*.

The determination of the virus etiology depends upon demonstrating a *rise in titer* of antibodies against the virus of either influenza A or influenza B. To demonstrate this rise in titer, it will be necessary to have *two specimens* of blood; one taken during the *acute illness* and the other taken *two weeks later*. *No examination* will be made of the *first specimen* unless the second specimen is received.

The Diagnostic Laboratory will be able to handle a *reasonable number* of specimens. Facilities are not available for examining an unlimited number. This is not necessary, of course, since it is an *exception* to the rule to have *more than one virus* highly *prevalent in an area* at one time. A few identifications of the type present in an area are all that are needed.

Special forms that should be used when blood specimens for serologic tests for influenza are sent in can be obtained by application to the Diagnostic Laboratory, 281 South Street, Jamaica Plain 30, Massachusetts.

MISCELLANY

INSURANCE FOR ALCOHOLICS

A survey to determine the stand insurance companies take on the insurability of applicants who have an alcoholic background is being conducted by the Keeley Institute of Dwight, Illinois.

Insurance companies, for the most part, turn down many applicants who have an alcoholic background, but who would otherwise be excellent risks, most of those rejected being actually alcoholics who have insight enough to recognize their condition and who have honesty enough to admit it. As with other ailments, such as diabetes, self-knowledge of alcoholism is of value in protecting the risk.

HAROFE HAIVRI

With the appearance of Volume II, 1948, *The Hebrew Medical Journal*, under the editorship of Moses Einhorn, M.D., concludes its twenty-first year of publication.

In publishing *Harofe Haivri* semiannually, the editors have met the need for a medical journal written in Hebrew, with English summaries, thus aiding greatly in the advance and development of Hebrew medical literature.

AMERICAN HEART ASSOCIATION

Dr. John W. Ferree has been named director of the Public Health Division of the American Heart Association, according to a recent announcement. Dr. Ferree will direct the development of public-health programs for the American Heart Association and will assist local heart associations in expanding and maintaining effective cardiac services in communities throughout the United States. He will supervise the Association's field staff now engaged in community organization and program development.

The formation of additional affiliated heart associations and the expansion of community services comprise an important objective of the American Heart Association's 1949 national campaign, from February 7 to 28, in which a total of $5,000,000 is being sought for a three-way program of research, education and community service.

CORRESPONDENCE

REGARDING EXTRARENAL AZOTEMIA

To the Editor: I have read with much interest the article by Appel and Townsend entitled "Extrarenal Azotemia: Report of a severe case with recovery" in the January 20 issue of the *Journal*. The case reported therein would, I think, fit very nicely a diagnosis of lower-nephron nephrosis with spontaneous recovery. More specifically, the patient had severe oliguria for about ten days, followed by a diuresis (he was excreting over a liter of urine by the second hospital day); he had a marked azotemia, and examination of the urine showed red cells, white cells and casts in the sediment. The vomiting (with loss of hydrochloric acid) and the voluntary reduction of fluid intake during the oliguric period may well account for the alkalosis and for the failure to form edema respectively. The case would fit quite well into the series of lower-nephron nephroses with spontaneous recovery reported by Strauss in the November 4 issue of the *Journal*.

WALTER HOLLANDER, JR.
338 Vanderbilt Hall
Longwood Avenue
Boston 15, Massachusetts

Mr. Hollander's letter was referred to Dr. James H. Townsend, senior author of the article in question, who made the following reply:

To the Editor: The point raised by Mr. Hollander is a good one. In the absence of any histologic examination, of course, we cannot say whether there may have been morphologic changes in the kidney. Because of the very slight changes in the urine and the promptness of the recovery following administration of salt and water we believed that there was little if any actual disease in the kidney.

The distinction between "extrarenal azotemia" and "lower-nephron nephrosis," I think, is very largely an academic one. In this case there had been no condition leading to shock or severe anoxia or any other dramatic episode to cause a nephrosis. We chose to call the disease extrarenal azotemia. If Mr. Hollander chooses to call it lower-nephron nephrosis, I should not object. The point is that this patient presented a severe picture resembling uremia that might well have been fatal and was very easily corrected by the simple administration of salt and water. He showed no evidence of any previous or permanent renal damage.

I have recently seen a somewhat similar case in another hospital that proved fatal and in which the kidneys showed no demonstrable lesion whatever. The patient was a catatonic schizophrenic who became extremely overactive and dehydrated and went into shock with azotemia and died.

JAMES H. TOWNSEND, M.D.
Mount Auburn Hospital
Cambridge, Massachusetts

NOTICES

ANNOUNCEMENTS

Dr. Sidney S. Gellis announces the removal of his office from 319 Longwood Avenue, Boston, to the Children's Hospital, 300 Longwood Avenue, Boston, for the practice of pediatrics.

Dr. Harold I. Shuman announces the removal of his office from 483 Beacon Street, Boston, to 92 Broadway, Taunton, for the practice of pediatrics.

Dr. Richard H. Wright announces the opening of his office for the practice of internal medicine at 1180 Beacon Street, Brookline.

SOUTH END MEDICAL CLUB

A regular luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 15, at 12 noon. Dr. George W. Thorn will speak on the subject: "Screening Tests for Adrenal Insufficiency."

All physicians are cordially invited to attend.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 23, at 8 p.m. The scientific program, entitled "Symposium on Thromboembolic Disease," will be as follows:

Physiologic Aspects of Intravascular Thrombosis. William C. Moloney, M.D.

Clinical Aspects of Anticoagulant Therapy. James A. Evans, M.D.

Surgical Aspects of Thromboembolic Disease. E. Everett O'Neil, M.D.

All physicians are invited.

NORFOLK DISTRICT WOMEN'S AUXILIARY

The Women's Auxiliary of the Norfolk District Medical Society will meet in the State Suite at the Copley Plaza Hotel, Boston, on February 28, at 2:30 p.m.

BOSTON SURGICAL SOCIETY

The monthly clinical meeting of the Boston Surgical Society will be held in co-operation with the Staff of the Paraplegia Service of Cushing Veterans Administration Hospital, Framingham, Massachusetts, on Friday, February 25. A symposium entitled "Some Aspects of Paraplegic Care" will be presented.

PROGRAM

Recreation Hall (9:30 a.m.)

Welcome and Introduction. Drs. R. R. Gasser and H. S. Talbot.

The Immediate Care of Patients Following Spinal-Cord Injury. Dr. Donald Munro.

Some General Metabolic and Hygienic Problems. Dr. Joseph W. O'Neil.

The Major Urologic Considerations. Dr. Arthur Bassell.

The Problem of Pain. Drs. John H. Van Landingham and John T. O'Neil.

Intermission — Visit to Ambulation Clinic (11:00 a.m.)

Ward (11:30 a.m.)

Demonstration of Tidal Drainage and Cystometry. Dr. Melvin K. Lyons.

The Surgical Treatment of Pressure Sores. Dr. Robert T. Steinsieck.

Discussion (12:00 m. to 12:30 p.m.)

For those who wish to remain, lunch will be served (60 cents) and there will be informal tours of the paraplegic wards and related departments after lunch. To facilitate adequate arrangements, guests who desire lunch should so notify Dr. H. S. Talbot, Cushing Veterans Administration Hospital, Framingham, Massachusetts, not later than Tuesday, February 22.

POSTGRADUATE INSTITUTE OF PHILADELPHIA COUNTY MEDICAL SOCIETY

The Philadelphia County Medical Society will hold its Thirteenth Annual Postgraduate Institute at the Bellevue-Stratford Hotel, Philadelphia, from April 5-8. The program has again been arranged on the basis of symposia, and the following subjects will be covered: diseases of the circulatory system, common conditions in the oral cavity, diabetes, anterior poliomyelitis, blood dyscrasias, diseases of the kidney, miscellaneous problems, pain, industrial medical and surgical problems, common obstetric problems, problems of infancy and childhood, eye, ear, nose and throat, gastrointestinal problems and vaginal discharge (causes and treatment).

There will be the usual number of high-grade technical exhibits.

The admission fee for the entire institute is $5.00. Programs will be available very shortly.

For further details application should be made to Gilson Colby Engel, M.D., Director, 301 South 21st Street, Philadelphia 3, Pennsylvania.

AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology does not evaluate, approve or disapprove any ophthalmic residency toward fulfilling the requirements for candidates for board examination. Any candidate who qualifies for the board examination and completes the prerequisites as outlined in the booklet of information will be accepted. A copy of this booklet can be obtained from the secretary of the American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN ACADEMY OF GENERAL PRACTICE

Application blanks for membership in the American Academy of General Practice may be obtained from the secretary of the Massachusetts chapter, Dr. James G. Simmons, of Fitchburg.

INTERNATIONAL AND FOURTH AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The meeting of the International and Fourth American Congress on Obstetrics and Gynecology will be held at the Hotel Statler (formerly, Hotel Pennsylvania), New York City, on May 14 to 19, 1950, under the sponsorship of the American Committee on Maternal Welfare.

The preliminary program for the scientific sessions will include morning meetings, Monday through Friday, May 15 to 19, of general sessions each devoted to one of the following five topics: physiology of human reproduction; pathology of human reproduction; social and economic problems; neoplastic diseases of the female reproductive system; and obstetric and gynecologic procedures. The afternoons will be given over to meetings of various groups represented at the Congress, including nurses, nurse midwives, hospital administrators, educators, practicing physicians, investigators in special fields and public-health doctors and nurses.

Applications for space in the scientific exhibit or for time on the motion-picture program should be submitted to the chairmen in charge of these activities on official application blanks obtainable from the business office of the International Congress at 24 West Ohio Street, Chicago 10, Illinois.

All inquiries pertaining to the meeting should be addressed to the chairman of the International and Fourth American Congress on Obstetrics and Gynecology, Dr. Fred L. Adair, at 24 West Ohio Street, Chicago 10, Illinois. Mr. Karl S. Richardson is business manager.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 7–APRIL 13. American College of Surgeons. Sectional Meetings. Page xi, issue of December 23.

FEBRUARY 14. New England Heart Association. Page 160, issue of January 27.

FEBRUARY 15. South End Medical Club. Page 239.

FEBRUARY 15. Greater Boston Medical Society. Page xvii, issue of February 3.

FEBRUARY 23. Norfolk District Medical Society. Notice above.

FEBRUARY 25. Boston Surgical Society. Notice above.

FEBRUARY 28. Norfolk District Women's Auxiliary. Notice above.

MARCH 7–9. American Academy of General Practice. Page 728, issue of November 4.

MARCH 10. Evaluation of the Treatments of Arthritis. Dr. Walter Bauer. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MARCH 28–APRIL 1. American College of Physicians. Page 158, issue of July 22.

APRIL 5–8. Postgraduate Institute of Philadelphia County Medical Society. Notice above.

MAY 4. New England Obstetrical and Gynecological Society. Springfield Country Club, Springfield.

MAY 16–19. American Urological Association. Biltmore Hotel, Los Angeles, California.

MAY 24–26. Massachusetts Medical Society. Annual Meeting. Worcester Memorial Auditorium, Worcester.

MAY 26–28. American Goiter Association. Hotel Loraine, Madison, Wisconsin.

MAY 30–JUNE 3. International Congress on Rheumatic Diseases. Page 800, issue of November 18.

JUNE 20–23. Annual Conference of Health Officers and Public Health Nurses. Page xvii, issue of February 3.

SEPTEMBER 28–30. Mississippi Valley Medical Society. Page 1060, issue of December 30.

NOVEMBER 2. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 11–17. Third Inter-American Congress of Radiology. Page 158, issue of July 22.

MAY 14–19, 1950. International and Fourth American Congress on Obstetrics and Gynecology. Notice above.

(*Notices concluded on page xvii*)